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A TEXT-BOOK

OF

PHARMACOLOGY

AND SOME ALLIED SCIENCES

(Therapeutics, Materia Medica, Pharmacy,
Prescription-Writing, Toxicology, etc.)

TOGETHER WITH

OUTLINES FOR LABORATORY WORK; SOLUBILITY AND DOSE TABLES, ETC.

BY

TORALD SOLLMANN, M.D.

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SECOND EDITION; THOROUGHLY REVISED AND GREATLY ENLARGED

PHILADELPHIA AND LONDON
W. B. SAUNDERS COMPANY
1908

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PREFACE TO SECOND EDITION.

PHARMACOLOGIC research has been active in the time which has elapsed since the publication of the first edition of this volume, and has added many details to our knowledge, and modified many of our conceptions. These additions and modifications are so dispersed over the entire subject-matter, that it seemed advisable to not only revise, but to practically rewrite, the book, in order to make it representative of the present status of the science. Further experience has also shown that many subjects could be profitably condensed or expanded, without sacrificing clearness or simplicity; and that the book could be made more useful to the advanced student, and for reference, without detriment to its primary object, as a text-book for beginners. Several new features have been introduced for this purpose.

Pharmacology Proper: The general arrangement and the pharmacologic system of classification are practically the same as those of the first edition. The "new" remedies have perhaps been accorded more attention than is justified by their intrinsic value; but their introduction seemed desirable for purposes of reference.

Laboratory Work: This has been entirely remodeled. The reception accorded to the short Exercises in the first edition has made it apparent that it is not only desirable, but quite feasible, to teach pharmacology largely by the laboratory method, and indeed, to make this the basis, rather than an adjunct, of the instruction. The course has, therefore, been considerably enlarged, systematized, and provided with explanatory notes, so as to make it entirely independent from the text, or rather, an introduction to the latter, as illustrated by the outlined summaries, page 940. The plan of the course is fully explained in the prefatory chapter, page 771. The description of the technic and apparatus has also been elaborated, for the guidance of the instructor and for the beginning investigator. It is hoped that the dose-tables for animals, page 945, will be a welcome addition.

Bibliographic References: A text-book can only summarize the main facts, and must neglect the details. This treatment suffices for elementary students; but advanced workers, who wish to delve deeper into the subject, must supplement the text by the original literature. The selected bibliography, page 978, is intended to serve as guide for this general collateral reading. The authority for specific statements of the text is indicated by the names of the investigators; the reference to the paper may be found in the alphabetic bibliographic register, page 1029.

A complete bibliography is neither practical nor desirable in a work of this character; a guide to the literature is all that can be furnished. For this reason, the emphasis has been laid on the more recent papers, which give citations of the older work. The latter has only been quoted directly, in addition to the later work, when it is of fundamental importance. I have tried, however, to include all the more important papers in the register, and believe that the alphabetical arrangement will be found convenient.

Materia Medica: This has been revised to conform with the eighth (1905) edition of the United States Pharmacopœia. The physical characters of the drugs can only be studied by direct contact; the other data are mastered most easily and thoroughly by requiring the student to collect, arrange and tabulate them. A series of schedules for such lessons, emphasizing the more important drugs, has, therefore, been introduced as Appendix A, page 961.

Pharmacy and Assaying have also been revised in conformity with the new Pharmacopœia.

General Toxicology: The data concerning the symptoms, etiology, isolation and treatment of poisoning, have been generalized in one chapter (page 79); the symptoms and treatment being given in detail under the heading of each drug, as in the first edition.

The tables of molecular formulæ and weights, and of solubilities (at 25° C.) (page 986), as also of the *average doses* (page 1011) are based on the revised Pharmacopœia. The dose-table made the retention of the doses in the *index* superfluous. Other changes in the index have been made with the object of convenience.

Illustrations: A considerable number of new cuts of tracings and apparatus have been added. The tracings are reproductions of actual specimens; a few having been redrawn and condensed, to economize space. The list on page 13 may be found convenient.

CLEVELAND, OHIO.

PREFACE.

One of the achievements of the latter half of the century just closed has been the development of the study of the action of drugs along lines scarcely dreamed of formerly. This has been made possible mainly by recourse to animal experimentation; by methods analogous to those upon which the modern science of physiology is built; by replacing accidental observation by well-directed research. Our knowledge has thereby been placed on a footing of exactness, without which the application of drugs to the treatment of disease could only be empirical.

The ever-growing importance of this new science has made necessary a revolution in the methods of teaching and studying. To understand the facts furnished by experimentation, to appreciate the course of reasoning which led to them, to give their proper value to new observations, the attitude of the student must become somewhat that of the original investigator. Discourses on the application of drugs to the cure of disease must be supplemented by discourses on the physiologic action of the drugs, on reasons for these actions, and on the experiments upon which the stated facts are based. These again should be supported by demonstrations or laboratory work, if possible. A want of this acquaintance with experimental methods has served to delay the recognition of the importance of pharmacology. It has also hampered the more intimate relation of this science with applied medicine—a relation which could not fail to be of the greatest benefit to both. Nor does the usefulness of pharmacology stop when it has explained the action of drugs. It has placed the treatment of poisoning, as well as that of disease, upon a rational basis. It has thrown light upon the nature of many diseases which are really intoxications. It has furnished the other sciences with methods and instruments of research.

The advantages of studying therapeutics in the light of pharmacology will scarcely need further recommendation. However manifest these advantages appear, it has greatly detracted from them that the facts furnished by pharmacology have been comparatively inaccessible. The bare statement of the conclusions of different observers is of use only if the underlying experiments are understood. Extensive text-books or technical journals are of use only to the specialist. Too great detail, indefinite statement, and conflicting theories only confuse the student.

To treat the subject apart from its practical application makes this application difficult. To treat it as an adjunct to clinical therapeutics deprives it of the logical arrangement which constitutes one of its chief advantages. The two, although interdependent, are best separated in the teaching. The former, the clinical application, belongs properly to the practice of physic. On the other hand, the subjects of pharmacognosy, pharmacy, materia medica, prescribing, incompatibility, toxicology, etc., in so far as they have any place in the medical curriculum, are conveniently taught from the same chair as pharmacology.

My aim in writing this volume has been to meet these objections and indications.

I have attempted to give all the important pharmacologic facts. To facilitate their understanding and memorizing, they have been arranged in a systematic and logical manner, and the detailed account of the actions has been prefaced by a very brief summary. To bring out the more important points, liberal use is made of display type, rendering it possible to insert considerable matter intended only for reference, without making the book unwieldy.

The experiments and reasoning which have led to conclusions are given in detail whenever necessary. A section on laboratory work has been added, giving a few simple experiments, together with suggestions which will permit of making them much more extensive. These require but little apparatus, and no difficulty will be experienced in introducing them in schools with a limited number of students. With larger classes they may serve as a basis for demonstrations. The study of these experiments, even if they cannot be actually performed, will serve to render clear to the student many points which he would otherwise find it difficult to comprehend; their description should therefore form part of the text-book.

When the statements of different observers vary, or when several theories are advanced, stress has been placed on those which deserve preference. Others, which are manifestly erroneous, have often been omitted entirely. Whenever it has been possible to give a theory which accounts satisfactorily for a number of facts, this has been done.

To each group is attached a short section treating of its therapeutic application. This is further made prominent by numerous compilations of drugs which may be used to secure a given result; of the members, manner of action, and indications of the older therapeutic groups; and by a number of summaries giving the treatment of common pathologic conditions. These summaries are intended rather to point out the application of pharmacology to practice, leaving the detailed treatment of therapeutics to text-books on physic. Frequent cross-references are introduced to avoid repetition, but the latter is practised when it has seemed advantageous.

The subject of materia medica is a vexatious one in medical teaching, from the difficulty of deciding how much matter should be included. This is still more true of a text-book intended at once for study and for reference. I have aimed to limit the information to that which is likely to be of actual use in prescribing. . . . Unofficial preparations in common use, or possessing advantageous features, have been freely introduced, preference being given to those of the "National Formulary."

The subject of pharmacy has been similarly restricted. Toxicology is discussed in conjunction with the pharmacology. A superficial knowledge of the course of toxicologic analysis is essential to the understanding of medicolegal questions. The identification of inorganic poisons receives sufficient treatment in text-books of chemistry. The organic poisons are generally omitted in these, and indeed often require pharmacologic experience for their recognition. A very brief outline of this subject has been given in a special chapter; similarly with pharmaceutic assaying.

CLEVELAND, OHIO.

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PART I.

THE PREPARATION AND PRESCRIBING OF MEDICINES.—TOXICOLOGY.

CHAPTER I.

A. GENERAL INTRODUCTION.

The term **Pharmacology** is used in a general sense to cover all scientific knowledge pertaining to drugs, *i. e.,* to substances which may be used in the treatment of disease. *Materia Medica, Pharmacognosy,* and *Pharmacographia* have the same meaning when they are used in a general sense.

General Pharmacology may be divided into five branches; authors differ in the names which they apply to these subdivisions. The following appear to be the most suitable for medical science:

1. **Materia Medica** *(Pharmacographia),* deals with the commercial and natural history of drugs; their physical and chemic characters; gross and microscopic anatomy; dosage. In this book, the term will also include the pharmaceutic preparations of the drugs. The term *Organic Materia Medica* is limited to the drugs derived directly from the vegetable or animal kingdom. *Pharmacognosy* generally signifies the anatomic and chemic structure of crude drugs.
2. **Pharmacy.**— The science and art of preparing drugs for medical use. Includes *Metrology* (weights and measures); *Manufacturing,* and *Dispensing.*
3. **Toxicology.**— Pharmacology applied to the study of poisons; their detection, effects, and treatment.
4. **Pharmacology proper** (*Physiologic Pharmacology, Pharmacodynamics*).— Concerns itself with the reactions occurring between drugs and living structures; often restricted to the experimental study of the action and fate of drugs in the animal organism. (Pharmacodynamics

is etymologically the most suitable term, but is unwieldy).

5. Therapeutics.— The practical application of Pharmacology and other sciences to the treatment of disease.

These five subdivisions comprise some minor branches, such as: Prescribing; Incompatibility and Solubility; Administration; Posology (Doses), etc.

For the systematic study of pharmacology, it is convenient to begin with pharmacognosy, pharmacy, and other preparatory subjects. In the study of pharmacodynamics, one may begin either with the drugs which act after absorption (Chapter VIII), or with those which act locally, wherever they are applied (Chapter XXVIII). The former is the more satisfactory if the entire course is to be finished within one year, and if the student has completed the study of physiology. Otherwise, it is advisable to omit Chapters VIII to XXVII until the other work is concluded.

B. ELEMENTS OF PHARMACOGNOSY.

PHARMACOGNOSY is that branch of science which treats of the structure and chemic character of drugs.

The crude organic drugs which form a large part of the materia medica are principally derived from the vegetable kingdom. All the different parts of a plant are employed. The active principle is often diffused throughout the plant, but is generally more abundant in one particular part, which is then used.

I. GROSS ANATOMY OF PLANTS.[1]

1. Underground Portions of the Plant.—*Root (radix):* that part, generally devoid of chlorophyl (green coloring-matter), which has not the power of producing leaves. Roots possess a bark, which is sometimes employed separately (sassafras, euonymus). If the underground portion does produce leaves, it is called *rhizome (rhizoma).* If part of the root serves for the accumulation of reserve food material, it becomes greatly thickened and is then called *tuber.*[2] If this accumulation takes place in the root-leaves, it forms a *bulb (bulbus).*[3] The lowest part of the stem of the plant is often thickened, and is then called *corm (cormus).*[4]

2. Portions Above Ground.— When the whole plant, with the exception of the root, is used, it is termed *herb* (*herba* or *species).* This consists of stems, leaves, and often flowers or fruits.

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[1] Consult Exercise 1.

[2] Potato.

[3] Onion.

[4] Colchicum.

Stem.— With herby plants this is called *stipes;* with larger plants it is transformed into *wood* (*lignum*) and is covered with *bark* (*cortex*). The outer (*epidermal*) layers of the older bark are always corky. Inside of this a secondary bark develops (*liber*).

The *leaves* (*folia*) may consist of a leaf-stem (*petiolus*) and the blade (*lamina*).

The shape of the leaves, the distribution of their veins, and the character of the edges are often of importance in distinguishing them.

The *flower* (*flos*) must be considered as a special modification of the leaves. It consists of the (usually green) *calyx* (parts = sepals), of the (usually colored) *corolla* (parts = petals) and of the less conspicuous male and female elements (*stamens* and *pistil*). The former bear the fertilizing element in the form of granules (*pollen*). The pistil consists of the *ovary,* which develops the *seed,* and the *style* and *stigma,* which serve to receive the pollen. The calyx, corolla, and pistil or stamina may be wanting.

After fertilization the ovary develops into the *fruit* (*fructus*); this may also involve neighboring parts, especially the top of the stem, as in the apple, strawberry, etc.

The fruit consists of the outer portion, *pericarp,* and the seed (*semen*). The latter contains the embryo and nutritive material. It is protected by a more or less hard shell.

When the embryo beigns to develop it differentiates into a rootlet, and a fleshy portion, *cotyledon,* which will form stem and leaves.

Certain organic drugs consist of the coagulated **juices** of the plant, and do not show any structure.

II. CHEMISTRY OF PLANTS.[1]

The *elementary,* or *ultimate, constituents* of plants are mainly C, H, O, and N; the chemical compounds formed from these, are called the *proximate principles* or constituents of the plant. These belong to the chemical groups of proteids, fats, carbohydrates, tannins, resins, alkaloids, glucosids, acids, terpenes, etc. The chemical structure of the plant constituents is in most cases but partly understood. Plants also contain various inorganic salts.

Plants, like animals, consist of cells. These determine to a large extent not only the physical character, but also the chemic composition, of the drug.

1. The *cell-contents* (which contain the nucleus) consist of protoplasm. This may present various **granular enclosures** consisting of proteids (*aleuron*), starch, fat, and

---

[1] Consult Exercise 3.

mineral salts (especially calcium oxalate). They may be amorphous or crystalline.

Allied to the proteid enclosures are the *chlorophyl granules.*

These consist of a colorless, spongy, proteid groundwork, containing in its meshes the chlorophyl pigment. The latter consists really of a mixture of green and yellow colors (chlorophyl and xanthophyl).[1]

These chlorophyl granules are found mainly in the higher plants, and serve in the presence of light to assimilate CO_2, and consequently to form starch, etc. The chlorophyl is insoluble in water, but soluble in alcohol, ether, etc. During the process of drying, especially if this occurs slowly, the pigment is acted on by acids, etc., developed under these conditions, and undergoes various changes, usually becoming brown.

Other portions of the plant may also contain *coloring-matter of various nature.* (See Exercise 3). These produce the brown, etc., color of the fluid preparations.

The *fat* seems to be deposited and formed much as it is in animals; *i. e.,* by the transformation of the protoplasm.

Fat and fixed oils are compounds of fatty acids and glycerin. The most important are:

FATTY ACIDS:		FATS:
Palmitic, $C_{16}H_{32}O_2$	$(= CnH_2nO_2)$	Palmitin, $C_3H_5(C_{16}H_{31}O_2)_3$.
Margaric, $C_{17}H_{34}O_2$		Margarin, $C_3H_5(C_{17}H_{33}O_2)_3$,
Stearic, $C_{18}H_{36}O_2$		etc.
Oleic, $C_{18}H_{34}O_2$.	(Glycerin $= C_3H_5(OH)_3$).	

They are greasy liquids or soft solids; when heated, they undergo decomposition, denoted by acrid vapors. They are insoluble in water or glycerin, sparingly soluble in alcohol, and freely soluble in ether, chloroform, benzin, carbon disulphid, petroleum, ether, turpentine, etc., (*fat solvents*).

Fat may be seen in the cells either as drops or as crystals. The fat is most abundant in seeds, and may form more than half of their weight.

Starch $(C_6H_{10}O_5)_n$ is produced as one of the first stages in the assimilation of CO_2. It occurs in the form of granules, usually showing a laminated structure around a center

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[1] It is interesting to note that the decomposition of chlorophyl and of hemoglobin gives rise to an identical product, $C_8H_{13}N$.

(hilus). The character of this lamination, as well as the average shape and size of the granules, are important in distinguishing between different plants (Fig. 1).

Starch can be easily recognized by the blue color which it gives with iodin. It is insoluble in all the ordinary solvents, but with boiling water, swells and forms a peculiar mixture (paste).

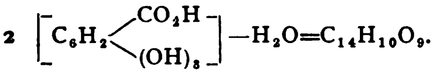
2. Besides these solid enclosures, the protoplasm may contain a large number of **substances in solution.** These may, however, also occur as precipitates under special conditions. In dried plants they occur, of course, as solids.

Tannins.— Under this name is comprised an ill-defined class of substances, derivatives of benzol, distinguished by giving a bluish or greenish color with ferric salts. The greater number also form insoluble compounds with other metallic salts, with alkaloid, proteids, etc. This precipitation leads to an astringent action.

The tannins have recently been classified by their chemic composition. More convenient is the older classification into:

1. *Physiologic Tannins.*— Occurring in normal plant tissues; giving a green color with iron; yielding pyrocatechin on dry distillation. Most of these tannins form with connective tissue an extremely insoluble and impermeable compound, and are therefor used in tanning.

2. *Pathologic Tannins.*— Occurring in pathologic tissues (galls); giving a blue color with iron (changed to green by acid); yielding pyrogallol on dry distillation; unsuited for tanning. Certain tannins are glucosids (*e. g.*, caffeotannic acids); others are not (*e. g.*, the ordinary (gallo-) tannic acid). The latter is the anhydrid of gallic acid.



$$2\left[C_6H_2\begin{matrix}\diagup CO_2H\\ \diagdown (OH)_3\end{matrix}\right]-H_2O=C_{14}H_{10}O_9.$$

Gallic acid. Tannin.

Tannins are soluble in water and in alcohol; but since they form insoluble compounds with so many substances, they often occur in plants in granular form.

Tannins are easily decomposed into resin-like bodies called *phlobaphenes.* These exist naturally in plants, but are usually found as artificial decomposition products in all extracts. They are dark-colored, soluble in alcohol and in alkaline liquids, insoluble in water.

Tannins and phlobaphenes, as well as most other plant constituents, are easily converted into a group of substances called *humins.* These do not exist in living tissues, and arise on the death of the cells, by the action of air and moisture. They cause the brown color which plants assume on drying; they are also present in the brown bark.

Tannins, phlobaphenes, and humins form a series, without sharp demarcation. They are not subject to the action of bacteria, and in this way protect plants against putrefaction.

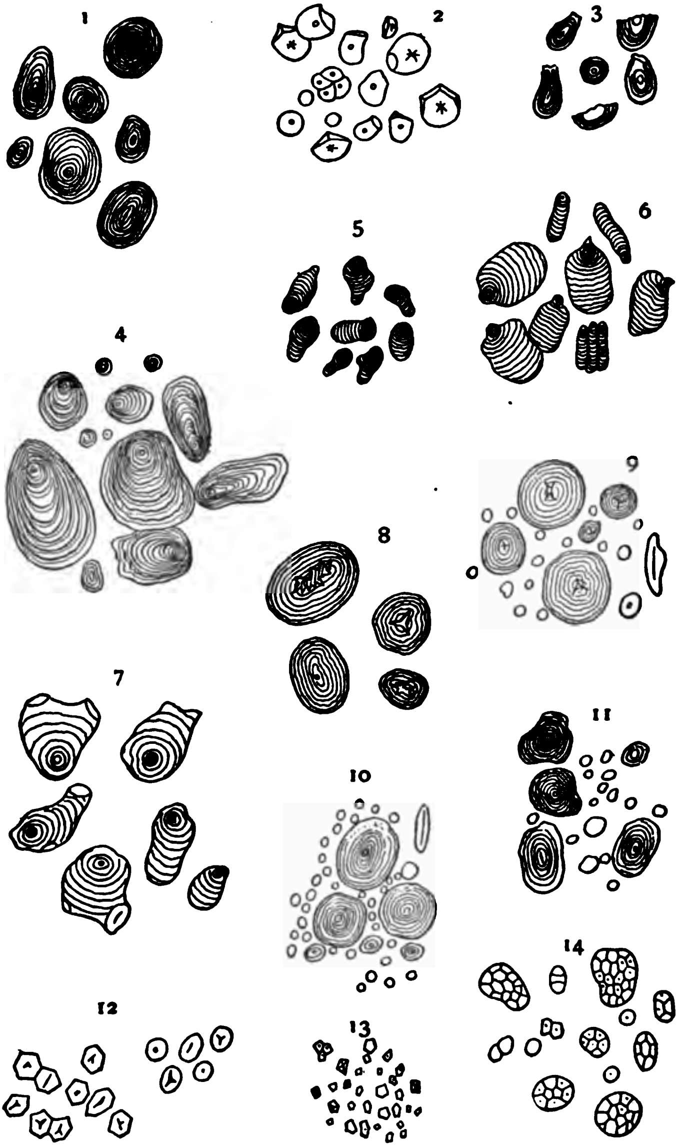


Fig. 1.—Microscopic appearance of different starches (uniform magnification) (Noël): 1, Arrowroot; 2, raw tapioca; 3, tapioca; 4, potato; 5, galanga; 6, East Indian arrowroot; 7, sago; 8, beans; 9, rye; 10, wheat; 11, barley; 12, Indian corn; 13, rice; 14, oats.

Proteids.— All the different classes are represented. They may be characterized by the biuret or Millon's reactions.

Sugar.— The various forms of sugars enjoy a wide distribution in the vegetable kingdom, and occur as cane-sugar, dextrose, levulose, and others. Some of these reduce copper in alkaline solution; others do so only after inversion. All turn the plane of polarized light. They are soluble in water; much less so in alcohol. The most important types are:

Glucose (Dextrose and Levulose), $C_6H_{12}O_6$; *Maltose* and *Saccharose,* $C_{12}H_{22}O_{11}$; *Mannite* $C_6H_{14}O_6$.

The other soluble carbohydrates of plants have, for the most part, the same empiric formula as starch ($C_6H_{10}O_5$). The most important are the *gums,* which give slimy solutions with water, and are insoluble in alcohol. *Pectins* are closely related substances, occurring in fruits, and causing the boiled fruits to set into jelly. Gums and pectins do not color with iodin; they reduce copper only after inversion.

Resins are compounds of uncertain compositions, non-volatile, soluble in alcohol, etc., insoluble in water and in petroleum ether. They are contained in special vessels, from which they are usually obtained as exudations after incising the plant. When they occur mixed with essential oils, they are *natural oleoresins;* when mixed with gums, *gum-resins.* If they contain aromatic acids (cinnamomic, benzoic, etc., or essential oils), they are called *balsams.*

Essential Oils (Volatile Oils) are odorous principles, of the physical characters of fatty oils, from which they differ by being volatile and soluble in alcohol. They are responsible for the odor of plants.

Chemically they belong to various groups, but the greater number are derived from turpentine ($C_{10}H_{16}$), and its polymers, $C_{15}H_{24}$, $C_{20}H_{32}$, etc. These constitute the part (*eleoptene*) of the oils which remains fluid on cooling; the solid portion (*stereoptene*) consists generally of oxidation products of the above ($C_{10}H_{12}O$ to $C_{10}H_{20}O$). A few oils also contain sulphur or nitrogen. The majority of oils are mixtures; some have the characters of esters, some of aldehydes, acids, alcohols, etc.

Alkaloids.— These comprise many of the most active and important plant constituents. They may be defined as natural nitrogenous organic bases; *i. e.,* they are organic substances, containing nitrogen, of basic character, combining with acids without the elimination of hydrogen, forming well-defined and usually crystalline salts. The salts with halogens are called hydrochlorids, hydrobromids, etc., (not chlorids, etc.).

Some alkaloids contain oxygen, others do not. Those containing oxygen are solid and comparatively non-volatile, whereas those free from oxygen (nicotin and coniin) are liquid and volatile.

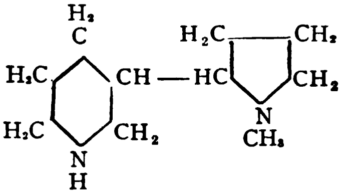
All alkaloids have certain *properties in common:* They have a bitter taste, turn red litmus paper blue, have a very profound physiologic action, and leave no postmortem changes. They are soluble in ether, chloroform, and oils, much less soluble in alcohol, and comparatively insoluble in water. Alkaloidal salts, on the other hand, have just the opposite solubility: They are soluble in water and alcohol, insoluble in chloroform and ether. With the alkaloidal salts, the combined acid plays a prominent rôle in the solubility.

Alkaloidal salts present the following *chemic reactions in common:*

1. The reaction for nitrogen.
2. They give precipitates with: Compound solution of iodin. mercuric-potassic iodid (Mayer's reagent); phosphomolybdic acid; picric acid; gold chlorid, platinic chlorid, etc. Many also precipitate mercuric chlorid, potassium bichromate, tannin, etc.
3. Many give color reactions with concentrated acids, with or without the addition of oxidizing or reducing agents.

The *chemic constitution* of alkaloids is not fully understood, but the greater number are built up from pyridin, quinolin, or pyrrol. The formula of nicotin may serve to illustrate their complicated structure. The elementary composition of the important alkaloids will be found in the appendix.

NICOTIN:



The *discovery of the alkaloids* is an achievement of the 19th century. (Morphin, by Sertuerner, 1805 to 1817; Strychnin, 1818; Quinin and Caffein, 1820; Nicotin, 1829; Atropin, 1833.)

Occurrence.— Only a few alkaloids occur in the animal kingdom, the most important example being epinephrin, the active principle of the suprarenal gland. Alkaloidal principles are also formed by the action of bacteria, and are called *ptomains.* Amongst the higher plants the occurrence of alkaloids is very common, the same plant containing usually several alkaloids, which are formed from one another. They are often found in all parts of the plants, but sometimes they are strictly localized in certain portions. Amongst seeds, *e. g.*, in aconite, in the central part; in physostigma in the cotyledons; in datura, hyoscyamus and atropa, in the layer beneath the epidermis; in nux vomica, both strychnin and brucin occur in the endosperm, brucin alone in the embryo.

Not all active vegetable principles are alkaloids. A large number have neither acid nor basic characters. These are called *Neutral Principles.* If these possess a markedly bitter taste, and are not very poisonous, they are termed *Bitter Principles.*

Glucosids are those principles which, subjected to the action of ferments or of acids, yield glucose as one of their decomposition products. Many do not contain nitrogen. Most glucosids are neutral, but a few are alkaloidal.

Saponins and *Sapotoxins* are neutral, non-nitrogenous bodies distinguished by foaming with waters, emulsifying oils, and laking red blood corpuscles. Many have the formula $C_nH_{2n-8}O_{10}$. Some are glucosids.

Resinoids are principles soluble in alcohol and insoluble in water. They are generally mixtures, often containing true resins.

Whatever principle determines the physiologic action of a drug is termed its *Active Principle.*

The juice of the plant contains dissolved in it a large number of organic compounds, such as *alcohols, aldehyds, ethers, acids, aromatic bodies,* etc.

Plants almost always contain *coloring-matter,* the chemic nature of which is often not known.

They also contain a fair amount of *mineral salts,* which remain as ashes when the plants are incinerated; these salts seem to be combined largely with the protoplasm, and exist partly dissolved, partly as crystals. Growing tissues are always richer in salts than those fully developed.

By *extractive matter* is meant the smeary mass of unknown composition which remains after evaporating any extract from which the important constituents have been removed.

Influence of the Time of Collection on the Constitution of Plants.— This factor is often very important. For instance, the activity of the leaves of digitalis and hyoscyamus is much greater in the second year of the plant than in the first. The unsprouted seed of strammonium contains fifteen times as much alkaloid as the sprouted seed; even the time of the day may make some difference, the leaves of the cinchona tree containing more alkaloid on bright days than on cloudy days or during the night. The best time for collection must be ascertained in each case, but as a general rule, roots are best gathered after the maturity of the plant; barks as soon as possible after they peel in the spring; flowers when they first open; seeds, leaves and herbs, just before they mature.

Certain important changes occur on **drying and storing.** These often cause deterioration (Ergot, Indian Hemp). On the other hand, they may be necessary to develop the therapeutic principle (Cascara, Podophyllum).

III. HISTOLOGY OF THE CELL.[1]

The form and arrangement of the cell walls determine the histology of the plant.

1. This **cell wall** consists originally of *cellulose.* This cellulose is chemically an isomer of starch, having the elementary formula $(C_6H_{10}O_5)_m$. It is insoluble in all the ordinary solvents, and is not affected by boiling water. It dissolves without change in Schweitzer's reagent (ammoniated solution of copper sulphate). In older cells it is often modified by the introduction of allied molecules: wood (lignin) or cork (suberin). The cellulose may also undergo a retrograde metamorphosis into gum or pectin.

A means of distinguishing between these compounds is the action of iodin after concentrated sulphuric acid: the tissue is treated with a drop of concentrated H_2SO_4, washed, and then placed in iodin solution; this will give a blue color to cellulose, but not to lignin or cork. Cellulose does not easily take up pigments, lignin does. Cork is very resistant to reagents and impermeable to water, and hence protects the plant against evaporation and chemic injury.

Under certain conditions cellulose seems to be converted into gum or pectins. This transformation may also involve the cell content. It occurs to some extent normally in certain tissues, but may become extremely abundant as the result of a pathologic process. The chemistry of these gummy substances is but imperfectly understood, but they belong to the carbohydrate group.

2. **Forms of the Cell.**— The cell may increase in size and in thickness, and assumes varying forms. The growth in thickness may remain confined to the walls, so that the lumen may be almost abolished. In either case it may not be uniform over the whole surface of the wall, and in this

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[1] Consult Exercise 2.

way depressions (pits) or elevations may be formed. The latter may assume various shapes, and occur as spirals, net-work, etc. (Figs. 2 and 3).

If the cell wall becomes very thick and the lumen correspondingly small, the result is a *stone cell* (Fig. 4).

3. The two **ground forms** of vegetable cells are:

Parenchyma (Fig. 5, and Fig. 6, *b*): Thin-walled cells of nearly equal diameters, rich in protoplasm, constituting the soft tissues.

Prosenchyma (Fig. 8): Thick-walled cells, lengthened, poor in protoplasm, found in all hard tissues.

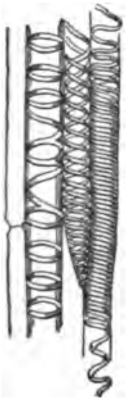

Fig. 2.— Spiral cell from squills (Flückiger and Tschirch).

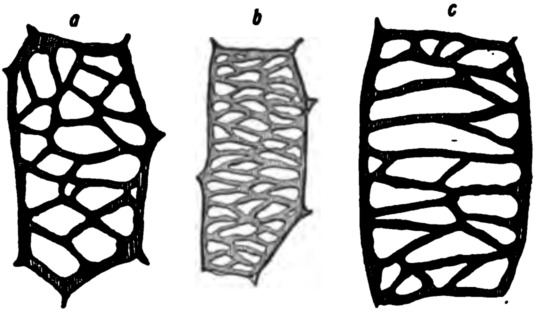

Fig. 3.— Reticular thickening of cell wall (Flückiger and Tschirch).

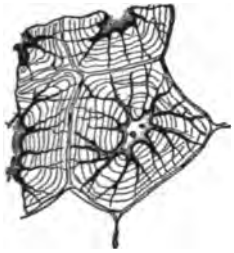

Fig. 4.— Stone cells from nutshell (Flückiger and Tschirch).

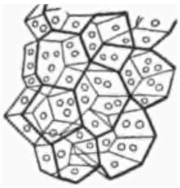

Fig. 5.— Parenchyma from elder pith (Flückiger and Tschirch).

IV. THE TISSUES.

The cells are united into tissues, which may be classified, according to structure and functions, into:

1. *Dermal:* for external protection.
2. *Supporting:* to give solidity.
3. *Assimilation:* for assimilation of CO_2.
4. *Conduction:* for the conveyance of juices.
5. *Storage:* for accumulation of reserve stock of water and nutritive material.
6. *Aeration:* for the conveyance of air.
7. *Glandular:* For the elaboration and storage of secretions.

1. Dermal Tissues.— The *epidermis* (Fig. 6, *a*) consists, in the higher plants, of one or more layers of flattened cells, generally possessing thickened walls, and covered by a structureless resistant membrane, *cuticle*.

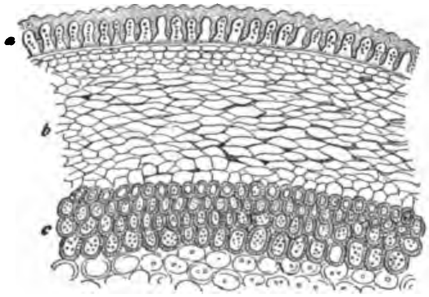

Fig. 6.— Fruit-shell of colocynth: *a*, Epidermis; *b*, parenchyma; *c*, sclerenchyma (Flückiger and Tschirch).

The epidermic cells may be transformed into *hairs* (trichomata) (Fig. 7). These may take on *glandular* functions (elaboration of the essential oils, resins, or gums); or they may be transformed into *spines;* but the latter generally contain wood also.

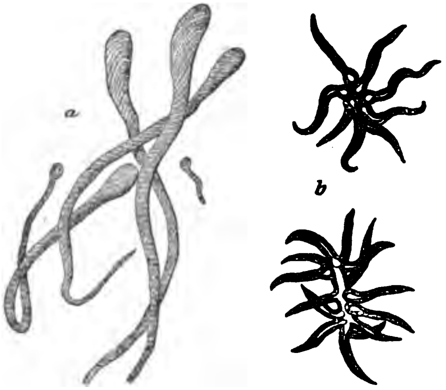

Fig. 7.— Hairs from mullein flowers: *a*, From stamina; *b*, from petals (Flückiger and Tschirch).

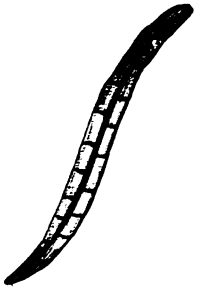

Fig. 8.— Bast cell from cinchona-bark (Flückiger and Tschirch).

This epidermis is the only covering of delicate plants; with the larger species it becomes insufficient. In these it is reinforced by the development beneath it of the *periderm,* which consists of cork cells. These are also flattened, thick-walled cells; they contain air and no protoplasm.

2. Supporting Tissues.— In younger tissues this function is borne by polygonal cells (*collenchyma*) with rather thick walls and containing protoplasm. In fully developed plants this is replaced by *bast cells* (*scleroids*) (Fig. 8); *i. e.,* long cells, similar to stone cells, with very thick walls and small lumen, containing air. They are variously arranged, occurring either isolated or combined into definite structures.

3. Assimilation Tissues (for CO_2).— These consist of the cells containing chlorophyl. Since assimilation of carbon occurs only in the presence of light, such cells are only found on exposed portions, especially in the leaves, and here on that side of the leaves turned toward the sky. The cells are of the parenchyma type, and are rich in protoplasm in which chlorophyl granules are embedded. The cells are usually arranged in palisade form.

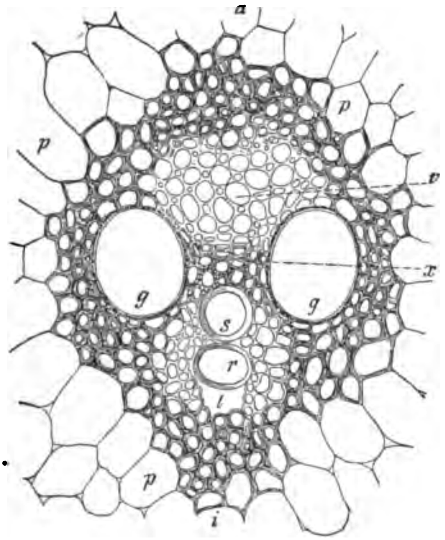

Fig. 9.— Transverse section through fibro-vascular bundle of maize stem: *a,* Exterior; *i,* interior; *p,* ground tissue; *r,* ring-vessels; *s,* spiral vessels; *g,* dotted vessels; *l,* intercellular cleft; *x,* wood cells; *v,* phloem (Sachs).

4. Conducting System.— The leaf-ribs, stems, and roots of plants are traversed by long fibrous structures, the *fibrovascular bundles* (Fig. 9). These consist of a number of conducting elements, surrounded and supported by bast cells. The former consists of several structures which may not all be present in the same bundle. These are:

(*a*) *The vessels proper.* These are long tubes, formed through the disappearance of the separating wall of adjoining cells. The walls of these tubes show various thickenings, which serve to classify them into ringed, spiral, ladder, etc., vessels. (Fig. 9, *r*, *s*, *g*.)

(*b*) The *tracheids* (wood cells). Each tube consists of a single long cell with rather heavy walls. These two sets of vessels serve for the conduction of water. (Fig. 9, *x*).

(*c*) *Wood parenchyma* (phloem). Short, thin-walled, protoplasmic cells, serving for the conduction and storage of carbohydrates. (Fig. 9, *v*.)

The *wood* (*lignum*) consists of these three elements, and of bast cells; all these are, on the whole, arranged in the long axis of the stem, but are traversed radially by rows of parenchyma cells (*medullary rays*). The youngest layer of the wood in dicotyledenous plants is the *cambium*, consisting of flat parenchyma cells.

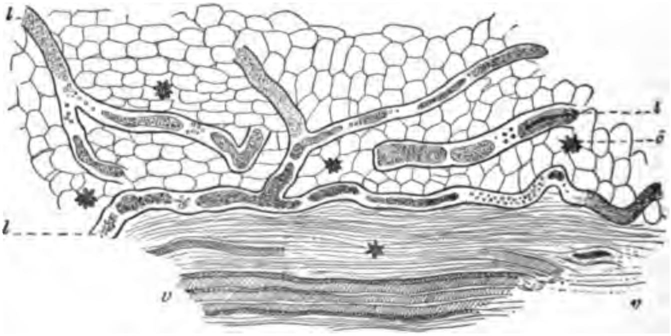

Fig. 10.—*l*, Lacteal vessels; *o*, calcium oxalate crystals; *v*, vascular bundles (Flückiger and Tschirch).

(*d*) Another element of the fibrovascular bundles is formed of the *sieve tubes*, very long cells, whose walls are formed by delicate membranes pierced with holes. They serve for the conduction of the albuminous elements.

5. Storage System.— Arrangements for the storage of reserve food material exist in the most varied organs. These reserve foods consist usually of solid and sparingly soluble substances: starch, fat, proteids, etc. Water is also stored. The storage takes place in the bodies of the cells forming these structures.

6. System of Aeration.— The gaseous metabolism of plants is very important. An extensive system exists for the penetration and distribution of gases. The epidermis, especially on the under surface of the leaves, is provided with pores (*stomata*), usually guarded by special cells, and these communicate with clefts in the tissue.

7. Glandular System.— This consists partly of cells, partly of tubes. The latter may be formed by the breaking-down of cell bodies, or as regular ducts, similar to those found in animal glands.

The *glandular cells* serve especially for the elaboration and storage of *ethereal oils*. They occur isolated and have a more or less globular form. Cells also serve for the elaboration and storage of mucilaginous and resinous substances.

Tubes.— The tubes for *milk juices* are partly conducting, partly glandular in function. They arise through the absorption of the separating membrane of cells, like the vessels of the vascular bundles, but usually occur isolated (Fig. 10.) These cells were originally filled with secretion: *caoutchouc* (differing from resin in being insoluble in ether), *alkaloids* (opium), *resins, oils*, or *balsams*. The side wall of the cell may also disappear, so that the contents lie in an intercellular space — resin or oil spaces (*e. g.*, oil of lemon)—(Fig. 11, *o* and *b*).

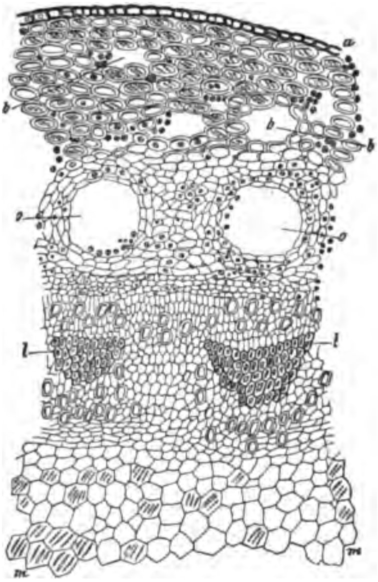

Fig. 11.— Oil spaces in transverse section of rhizome of *Arnica montana*: *l*, Wood-bundles; *o*, oil spaces; *b*, in process of formation by tearing of the ground tissue; *a*, epiblema (root-epidermis). Free oil drops are to be seen in the neighborhood of the oil spaces.

These differ in the manner of their formation from the *secreting spaces* (Fig. 12, *hg*), which were never cells, but represent from their origin ducts like those found in animal glands, and are surrounded by special parenchymatous secreting cells (Fig. 12, *c*). This formation is especially common in the umbelliferæ, compositæ, and coniferæ, in which they contain resins and essential oils.

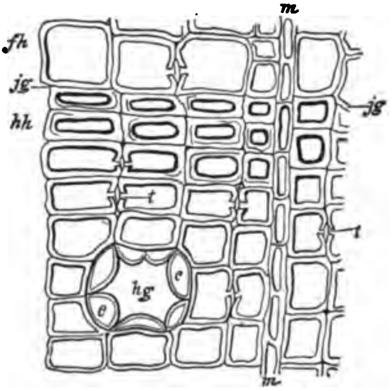

Fig. 12.—Cross-section of pine-wood: *jg*, Annual rings; *fh*, spring wood; *hh*, fall wood; *hg*, resin duct; *c*, secreting cells; *t*, pores; *m*, medullary rays.

CHAPTER II.

PHARMACY; METROLOGY.

1. Definition and Objects.—*Pharmacy* deals with the preparation and compounding of drugs for the purpose of administration.

The necessity for such an art will be readily understood. Drugs may be divided according to their origin into mineral, vegetable, and animal drugs. The last two are often too bulky to be conveniently used, and the substances which determine their action are often in such a condition that they can not readily be separated in the body, and so can not develop their action. Further, one drug alone does not usually meet all the indications in a disease, and when several are given it is necessary to combine them in such a way that they may not interfere with one another, either chemically or mechanically. Lastly, having chosen and prepared the drugs in a proper manner, and having decided how to combine them, it is highly desirable to give them in such a form as will be least objectionable to the taste, smell, or sight of the patient.

These constitute the objects of pharmacy: the separation of the active principles of drugs, their combination, and the putting of them in a pleasant form. In regard to the preparations, only those of the drugs of organic origin —

the "Galenics,"[1] so called — will be treated of in this place. The preparation of inorganic and synthetic compounds belongs more strictly to the domain of chemistry.

A certain degree of uniformity in the strength and preparation of pharmaceutic products is absolutely indispensable. Accordingly, practically all civilized countries have standards established by law, to which the drugs and preparations in the shops must conform. The book in which these standards are published is usually called the *Pharmacopœia*. That of the United States was first published in 1820, and is revised every ten years by a committee of physicians and pharmacists. Preparations made in conformity to it are called official.

The present "Eighth Decennial Revision" appeared during the summer of 1905 and became official on September 1, 1905. The title is commonly abbreviated to "U. S. P., 8," that of the British Pharmacopœia to "B. P."

The pharmacopœia deals only with standard remedies in common use. Many other preparations are also employed. The formulæ for these are usually taken from other standard works, e. g., the "National Formulary" (N. F.). Reference books which commend and enlarge on the pharmacopœia and formularies are called *"Dispensatories."*

In making pharmaceutic preparations, as also in "filling" prescriptions, the ingredients are combined in definite proportions, by weight or measure.

A discussion of the elementary principles of metrology, the science of weights and measures, then, forms the first topic treated of in this chapter.

2. Metrology.[2]— Formerly every country, even every State, and some cities, had their own system of weights and measures, resulting in endless confusion and loss of time. This state of affairs still exists to some extent. In the United States and Great Britain no less than five different systems are in common use. It is a hopeful sign that the United States Pharmacopœia has decided to employ the metric system. This system originated in France near the close of the last century. It has been adopted in science to the exclusion of all others, and possesses a number of advantages which should cause all other systems to be discarded. This is the present tendency, and the student who looks a few years into the future is urged to learn the doses and practice prescription-writing in the metric system. Since, however, the common systems are still used in some hospitals and journals, the equivalents on page 38 should also be mastered, and the conversion of the systems practiced.

A. The Metric System.— This is based on the decimal system, and has for the unit the measure of length, the meter (M.).

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[1] "Galenics" are, strictly speaking, medicines prepared after the formulas of Galen. The term is now used to designate standard preparations containing one or several organic ingredients.

[2] Consult Exercise 4.

This was intended to be a natural unit, viz. the ten-millionth part of the distance from the pole to the equator of the earth at a particular meridian. Subsequent measurements have given a slightly different value to this distance. The meter is therefor an arbitrary standard — the length of a platinum bar, the original of which is preserved in Paris.

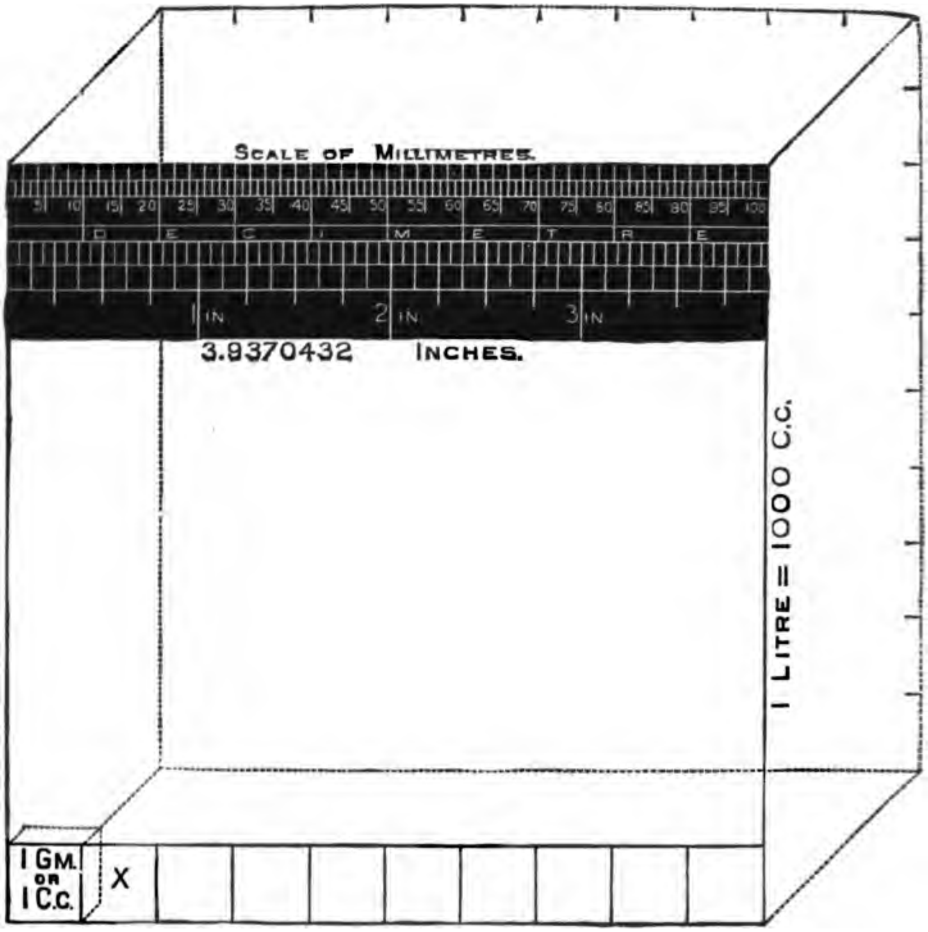

Fig. 13.— Metric diagram — comparison of measures of length, capacity, and weight (Coblentz).

The meter is divided into 10, 100, and 1000 parts, called respectively decimeter (dm.), centimeter (cm.), and millimeter (mm.).

The contents of a cube whose edges measure a decimeter form the unit of capacity (Fig. 13), the liter (L). The thousandth part of this is a cubic centimeter (c.cm., or, briefly, c.c.). The unit of weight is given by the weight of a liter of distilled water at 4° C. in vacuo: this is the kilogram (Kg.). A thousandth part of this is a gram (Gm.). A quantity ten times the unit is expressed by prefixing the Greek numeral Deca; one hundred times, Hecto; one thousand times, Kilo. The tenth part of the unit is expressed by prefixing the Latin numeral deci; one-hundredth, centi; one-thousandth, milli.

Thus:

1000 Gm. = Kilogram (Kg.)[1]
100 “ = Hectogram (Hg.)
10 “ = Decagram (Dg.)
1 “ = Gram (Gm.)
0.1 “ = decigram (dg.)
0.01 “ = centigram (cg.)
0.001 “ = milligram (mg.)

In quantities including several denominations only one unit is used: thus, 1.234 Kg. would be read as 1234 Gm.; 0.002 Gm. as two milligrams, etc. The quantities are always denoted by Arabic figures placed before the appellation. Fractional parts are always converted into decimal fractions.

In continental Europe the liquid measure is very little used in pharmacy, liquids being usually weighed.

Table I: Common Systems of Weights and measures.[2]

The denominations are the following:

APOTHECARIES' OR TROY WEIGHT.

(USED IN PRESCRIPTIONS.)

Grain (gr.)
[Scruple, (℈) = 20 grs.]
Drachm, (ʒ) [= 3℈] = 60 grs.
Troy ounce, (℥) = 83 = 480 grs.
[Troy pound = 12℥ = 5760 grs.]

(℥j of water under standard conditions[3] measures 504.83 minims.)

AVOIRDUPOIS WEIGHT.

(A SYSTEM USED IN COMMERCE.)

Grain = same as Troy grain.
Ounce (oz.) = 437½ grains.
Pound (lb.) = 16 ozs. = 7000 grains.
Ton = 2000 lbs.

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[1] Some authors begin all the abbreviations with capitals; others employ capitals for the units gram, liter and meter, and their multiples; and small letters for fractions (as in the above list); the latter plan has some advantages.

[2] Those in square brackets are practically obsolete.

[3] At 4° C. and in vacuo.

UNITED STATES APOTHECARIES' OR WINE MEASURE.

(USED IN UNITED STATES FOR BOTH PRESCRIPTION AND COMMERCIAL PURPOSES.)

Minim (♏) (approximately equal to one drop or to one grain of water — more exactly, 0.95 grain).

Fluidrachm (flʒ) = 60 ♏.
Fluidounce (fl℥) = 8 flʒ = 480 ♏ (fl℥j of water under standard conditions[1] weighs 456⅖ grains).
Pint (pt., or Octarius, O) = 16 fl℥ = 7680 ♏.
Quart (qt.) = 2 pts. = 32 fl℥.
Gallon (gal., or Congius, C) = 8 O = 128 fl℥ = 61,440 ♏.
A gallon holds 231 cubic inches.

Another system of liquid measure is in use in *Great Britain,* and must not be confused with the American system. It is the

IMPERIAL MEASURE.

		UNITED STATES SYSTEM.
Minims (min.)	=	0.96 ♏
Fluidrachm (fl.dr.)	= 60 min.	= 0.96 flʒ
Fluidounce (fl.oz.)	= 8 drachms	= 0.96 fl℥
Pint (O)	= 20 fluidounces	= 1.2 O
Gallon (C)	= 8 pints	= 1.2 C

In writing the apothecaries' measure in prescriptions, the figures are written in the Roman system and placed after the appellation. Thus, gr. xx, not 20 grs. The ones are always dotted, and the last one is formed like a j: thus, ʒiij, ℥vj, etc. The fl. before the sign is often omitted with liquids.

Fractions are written as common fractions: gr. $^1/_{10}$, not gr. 0.1.

Popular Measures.— These are formed of utensils commonly found in the household, and are, of course, very inexact. They should be displaced by graduated medicine glasses, which can now be obtained very cheaply. Spoons are supposed to be filled so that the fluid stands level with the rim.

The usually accepted equivalents of these measures are:[2]

1 drop (gtt.)	= 1 minim[3]	= 0.05 c. c.
1 teaspoon	= 1 flʒ[4]	= **4** or 5 c. c.
1 dessertspoon	= 2 flʒ	= **8** or 10 c. c.
1 tablespoon	= 4 flʒ (½℥)	= 15 or **16** c. c.
1 wine-glass	= 2 fl℥	= 50 c. c.
1 tea-cup	= 4 fl℥	= 125 c. c.
1 tumbler	= 8 fl℥	= 200 c. c.
1 knifepointful (tableknife)	= 15 to 30 grs.	= 1.0 to 2.0 Gm.

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[1] At 4° C. and in vacuo.

[2] The equivalents in heavy type are those recognized by the U. S. P.

[3] As a matter of fact, the size of a drop varies greaty according to the nature of the fluid and of the container; there may be from 50 to 150 to a fluid drachm.

[4] Really from ½ to 2 flʒ.

3. The **units of temperature** may also be treated in this place.

The scientific scale is the *Centigrade* or Celsius. In this the range between the freezing-point of water (0° C.) and its boiling-point (100° C.) is divided into 100 parts. In the *Fahrenheit* scale, in common use, the freezing-point of water is 32° F., the boiling-point 212° F., and the range, therefore, 180° F.

Each degree Centigrade therefore $= {}^{180}/_{100} = {}^{9}/_{5}$° F.
Each degree Fahrenheit $= {}^{5}/_{9}$° C.

The *conversion* of one scale into the other may be done by the following *rules:*

To convert degrees Centigrade into Fahrenheit: multiply by ${}^{9}/_{5}$ and add 32.

To convert degrees Fahrenheit into Centigrade: subtract 32 and multiply by ${}^{5}/_{9}$.

4. The **advantages of the metric system** will now be manifest.

1. The metric system is widely used, and is understood throughout the civilized world.

2. There is a simple relation between linear, solid, and liquid measures.

3. The decimal feature determines great ease in multiplications, since only a change of a decimal point is required to change one denomination into another. It is also much easier to write the quantities.[1] Calculations involving specific gravity are also much more easily made.

4. The adherents of the common system claim that it is more convenient. There may be some truth in this, for the grain, minim, and drachm happen to be more convenient doses than the gram or cubic-centimeter. This advantage, however, is insignificant.

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[1] An example will make this clearer: Take 40 Gm.: in the United States system this must be written ℥j ʒij gr. xvij. Should it be necessary to calculate five times this quantity, one multiplication will suffice with the metric system: 5 × 40 = 200 Gm. But with the Apothecaries' system, the operation would be much more complicated:

5 × ℥j ʒij gr. xvij = ℥v ʒx gr. lxxxv

This must be reduced:

℥v = ℥v
ʒx = ℥j ʒij
gr. lxxxv = ʒj gr. xxv

Answer = ℥vj ʒiij gr. xxv

5. Table II.—Equivalents of Metric and Common Systems.[1]

SPACE.

1 meter = 39.370 inches.	1 inch = 0.0254 M. = 2.54 cm.
= 3 ft. 3.370 inches.	1 ft. = 30.227 cm.
= 1 yd. 3.370 inches.	1 yd. = 91.440 cm.

CAPACITY (UNITED STATES).

1 c.c. = 16.23 ♏.	1 ♏ = 0.06161 c.c.
1 L. = 33.815 fl℥.	1 flʒ = 3.7 c.c.
= 2.113 pts.	1 fl℥ = 29.574 c. c.
= 0.2642 gal.	1 pt. = 0.4731 L.
	1 gal. = 3.7854 L.

CAPACITY (BRITISH).

1 L. = 1.760 pints.	1 pint = 0.5679 L.
= 0.2209 gallons.	1 gallon = 4.5435 L.

WEIGHT.

1 mg. = 1/64 gr.	1 gr. = 64.8 mg. = 0.0648 Gm.
1 Gm. = 15.432 grs.	1ʒ = 4 Gm.
= 0.03527 oz. Av.	1 oz. Av. = 28.3495 Gm.
= 0.03215 ℥ Troy.	1 ℥ Troy = 31.1035 Gm.
1 Kg. = 2.2046 lbs.	1 lb. = 0.4536 Kg.

The following approximate equivalents will be found sufficient for most purposes, and should be memorized:

APPROXIMATE EQUIVALENTS.

1 Gm. 1 c. c. } = 15.5 grains or minims.	1 grain or minim = 0.065 Gm. or c. c.
1 milligram = 1/64 grain.	1 drachm = 4.0 (—)
1 Liter = 1 quart (+).	1 ounce = 30.0 (—)
1 Kilogram = 2.2 lbs.	1 pint = 0.5 Liter (—)

INSTRUMENTS AND METHODS OF METROLOGY.

6. Weighing.—In determining the weight of a body, we balance the force which it exerts by virtue of its gravity, against another known force.

This is done by means of a balance, or, as it is called when used for larger masses, a scale. These are constructed on either the spring or lever principle.

The *spring balance* does not allow of any great accuracy, but has the advantage of cheapness and is very convenient.

The extent to which a spring is stretched by a given weight is determined experimentally, and a scale constructed in this manner (see Fig. 14).

The *lever or beam balance* compares the weight of a substance with a known weight suspended from the other side of the fulcrum. The arms of the lever may be *equal* (Fig. 15), when the weights on the two sides must also be equal in order that they may balance (equal-arm balance). The fine scales are usually constructed on this principle.

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[1] The student should be thoroughly drilled in the conversion of one system into the other. This requires some home-practice.

Or the arms may be unequal length, when the weight is given by the formula $L W = L' W'$; where L = length of beam and W the weight: *i. e.,* if W is 1 and L is 1, then if $L' = 2$, W' will be ½.

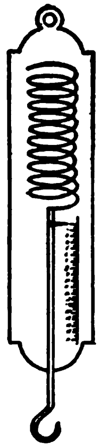

Fig. 14.— Diagram of spring balance.

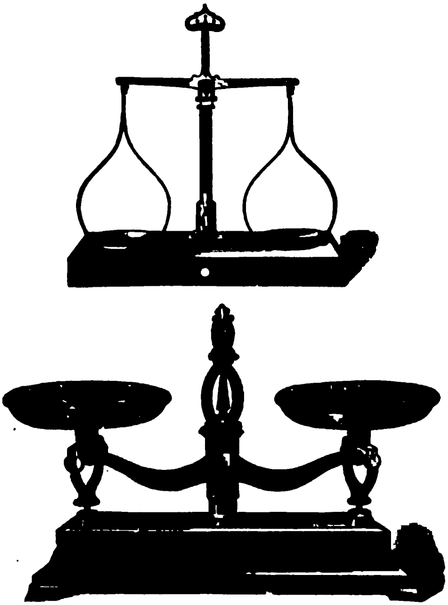

Fig. 15.— Equal-arm balances.

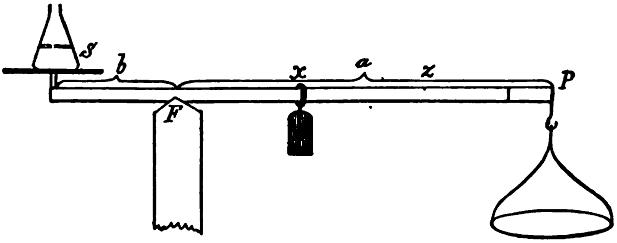

Fig. 16.— Diagram of unequal-arm balance.

The advantage of this arrangement lies in the fact that but one weight is required, the weighing being done by shifting this on the beam. Figure 16 illustrates a scale built on this plan. If the weight S is balanced with W at x, then twice S will be balanced at z, etc. This principle is also employed in weighing very heavy substances. If the distance $F P = 10 \times F S$, then each Gm. placed on the pan P will indicate 10 Gm. on S, etc.

The same principle is used in the *rider* of analytic balances. The arm is here divided into ten parts; a rider of platinum wire weighing 0.01 Gm. can be shifted along this arm, and each division will, of course, indicate $^1/_{10}$ of 0.01 Gm. = 1 milligram.

Some *mechanical features* in the construction of balances deserve further mention:

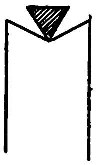

Fig. 17.— Knife-edge.

The fulcrum consists, in most balances, of a sharp prism of steel or, in better balances, agate,— the so-called *knife-edge,* — supported on a steel or agate rest (Fig. 17). The pans are suspended from similar knife-edges. It is essential that these three edges should be exactly parallel, else the shifting of the position of the weight on the pan will make a difference.

In the *torsion balance* the fulcrum is formed by a tightly stretched wire firmly fixed to the beam and supporting it. The movements of the latter cause torsion of the wire. This avoids the wearing of the knife-edge.

In the finer balances a *pointer* is attached to the center of the beam to facilitate the observation of its movements. It is not necessary to wait until the pointer comes to rest; balance is secured when it swings to the same extent on each side.

Two screws at the ends of the beam permit of balancing the two arms. Some mechanism exists in all balances for arresting the swing of the beam.

Liquids are weighed by counterbalancing (taring) the empty container, placing the required weight on the other scale-pan, and then adding the liquid until the balance is restored.

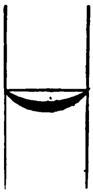

Fig. 18.— Meniscus.

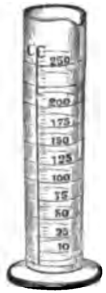

Fig. 19.— Cylindric graduate.

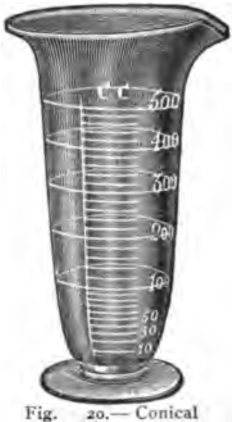

Fig. 20.— Conical graduate.

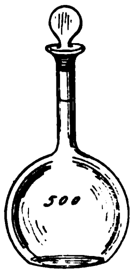

Fig. 21.— Measuring flask.

7. Measuring is done in graduated vessels, usually of glass ("graduates"). Several points must be kept in mind: The vessel containing the liquid must be held so that the level of the liquid is in a perfectly horizontal plane, and at the same height as the eye. This is greatly facilitated by having the marks encircle the graduate. The possibility of error is the greater, the broader the surface.[1] Owing to capillary attraction, the surface of the liquid is always cupped, producing the "meniscus" (Fig. 18). The reading should be taken at the lowest level of the meniscus. *Measuring flasks* and *"graduates," i. e.,* the vessels used for measuring larger quantities, are graduated for contents: *i. e.,* the quantity read is the quantity contained in them. Whilst pipettes and burettes are graduated for outflow: the quantity read is the quantity which will flow from them.

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[1] Greater accuracy may therefore be attained if the measuring vessel is as narrow as possible where the reading is taken.

Since the volume of liquids varies with the *temperature,* readings should be made at the temperature for which the measures are adjusted — approximately room temperature.[1]

Graduates are of two shapes, cylindric (Fig. 19) and conical (Fig. 20). Each has its advantages. The former, which is usually employed in scientific laboratories, allows measuring the liquid with equal accuracy at all heights. The conical graduate, on the other hand, allows smaller quantities to be measured with greater accuracy than larger ones, and facilitates cleaning. Measuring flasks are the only accurate method of measuring large quantities of liquids, since the reading part is very greatly constricted (Fig. 21).

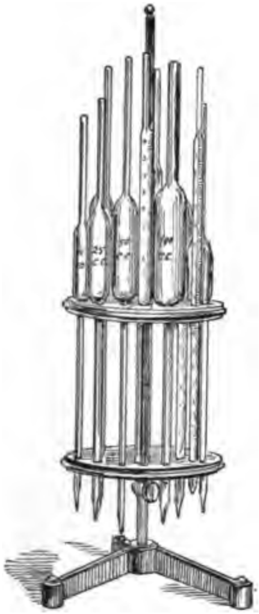

Fig. 22.— Pipettes.

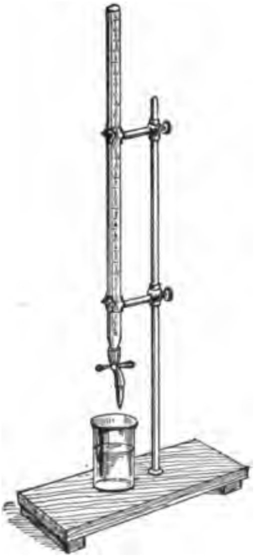

Fig. 23.— Burette.

For smaller amounts *pipettes* (Fig. 22) and *burettes* (Fig. 23) are employed.

To facilitate the reading of the latter *Erdmann's float* (Fig. 24) is a very convenient aid. The reading is made from the mark on the float. A cheaper way is to use a card with a horizontal line which is adjusted to the lowest part of the meniscus.

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[1] The present U. S. P. directs 25° C.= 77° F.

A topic closely related to this of metrology is that of

8. Specific Gravity.—This may be defined as the ratio of the weight of a given substance to the weight of an equal volume of a standard. The U. S. P. standard for liquids or solids is (in pharmacy) distilled water at 25° C. (77° F.), the specific gravity of the liquid being taken at the same temperature.[1]

Methods of Determining Specific Gravity.—

In principle, the weight and volume of the substance must be determined. Since 1 c. c. of the standard (water) weighs 1 Gm., it is only necessary to divide the weight in grams by the volume in c. c. to obtain the specific gravity.

$$\text{Sp. G.} = \frac{\text{W (Gm.)}}{\text{V (c. c.)}}$$

The details must vary with the physical nature of the substance.

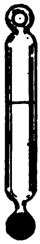

Fig. 24.—Erdmann's float.

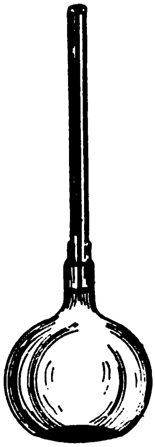

Fig. 25.—Pycnometer.

I. Liquids.—1. *Pycnometer* (Fig. 25).—A flask whose net weight is known, and also its weight when filled to the mark with water at 25° C., is filled with the liquid whose specific gravity is to be determined, and again weighed.

Example:

Weight of pycnometer filled with water = 56.5511
" " " empty = 27.0758
" " water = 29.4753
Weight of pycnometer filled with liquid = 60.2476
" " " = 27.0758
" " liquid = 33.1718
Specific gravity of liquid $= 33.1718 \div 29.4753 = 1.1254$

This is the most accurate method of determining the specific gravity of liquids.

2. By the *loss of weight of a solid.* A body immersed in a liquid

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[1] Alcohol is the only exception to this, its specific gravity being taken at 60° F. The solubility data of the U. S. P. also refer to 25° C.

loses the weight of its own volume of the liquid. The determination is done most conveniently with a specific gravity balance (Fig. 26).

Example:

A 50 Gm. weight weighs in distilled water 24.36 Gm.
Loss of weight = 25.64 Gm. = volume of the weight.
The same weight weighs in the liquid 20.15 Gm.
Loss of weight = 29.85 Gm. = weight of equal volume of fluid.
Specific gravity $29.85 \div 25.64 = 1.164$.

3. *Areometers* (Fig. 27).— These are adjusted to sink in the liquid to the mark on the stem corresponding to the specific gravity of the liquid. They are not usually very accurate, but are very convenient for ordinary purposes, such as the clinical examination of urine, etc. (urinometer). Formerly they were graduated in artificial scales, but at present they are made so that the specific gravity may be read off directly.

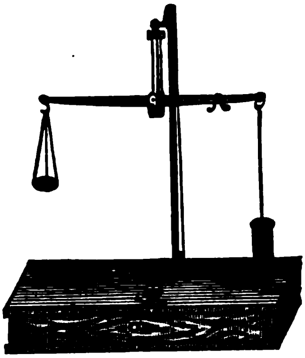

Fig. 26.— Specific gravity balance.

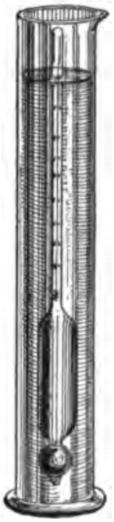

Fig. 27.— Areometer.

II. Solids.— These are weighed in the usual manner. The method used for the determination of the volume must vary in different cases. Into this we need not enter.

The specific gravity is of use in *calculating the weight or volume of substances:*

To determine the weight of a given volume of a substance, multiply this volume by the specific gravity: weight = volume × specific gravity.

To determine the volume of a given weight, divide the weight by the specific gravity: $\text{volume} = \frac{\text{weight}}{\text{specific gravity}}$

A term which is sometimes used is the *"specific volume,"* the volume of a substance compared with the volume of the same weight of the standard. It is the reciprocal of the specific gravity;

$$\text{specific volume} = \frac{1}{\text{specific gravity}}.$$

CHAPTER III.

PHARMACEUTIC METHODS.[1]

In the making of pharmaceutic products very different methods must be used, depending upon the physical and chemic nature of the crude drug, and upon the character of the desired product.

These may be roughly classified into those used in the making of many different preparations,— *general methods,* — and those used in only a very limited number of cases — *special methods.*

The methods can be best understood when studied in the order in which they are usually applied to the drug.

I. PREPARATORY PROCESSES.

Desiccation or Drying.— This is usually the first operation to which the crude drugs are subjected after their collection. It serves a threefold purpose: It reduces the bulk, assists preservation, and facilitates comminution.

Formerly the drying was done by spreading or hanging the drugs in airy lofts. At present they are usually placed on perforated trays in special drying closets and heated artificially (steam, etc.). They are often cut into smaller pieces before this drying. The degree of heat must not be so high as to injure the sometimes very unstable ingredients.[2]

Comminution.— The next step is comminution, or reducing of the substance to smaller pieces.

This is usually done by machinery. Crude vegetable drugs are first sliced or chopped, often before drying. They are then bruised by pounding in a mortar and finally ground, the finer grades of powders often several times, the grinding surfaces being brought closer together each time. The mills for this purpose are constructed on the same general principles as flouring mills, employing stones, rollers, etc. The details of the process used depend upon the physical character of the drug. A fibrous material like licorice root requires a different process from a friable substance like gum acacia.

On the small scale, drug mills, constructed more or less on the principle of the coffee-mill, are used for fibrous, and mortar and pestle for friable drugs. Mortars are made of iron, wedgewood, porcelain, and glass. (Fig. 28.)

---

[1] Exercise 5.

[2] The U. S. P. designates 32 to 39° C. as "gentle heat."

Trituration is the process of rubbing (not pounding) a substance to a powder in a mortar.

Some points deserve special mention. Often a substance will not powder by itself, but will do so when mixed with another substance — *e. g.*, sugar of milk. This is called "pulverization by intervention." Sometimes it is well to moisten the drug — *e. g.*, camphor with alcohol, nux vomica with steam, etc.

In the process of percolation, presently to be described, it is often essential to use a powder of a certain degree of fineness. The powders are therefore sifted, and are classified according to the size of the meshes of the sieve through which they pass, thus:

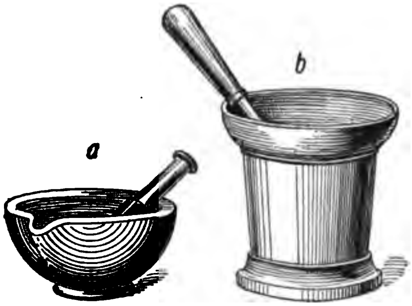

Fig. 28.— Mortars: *a*, Wedgewood or porcelain; *b*, iron.

No. 80 = 80 meshes to linear inch, very fine.
" 60 = 60 " " " " fine.
" 50 = moderately fine.
" 40 = " coarse.
" 20 = coarse.

Since the different structures in a crude drug do not powder with equal readiness, it is essential that the whole of the drug to be powdered should be passed through the sieve, else the different portions will not have the same composition.

To obtain very fine powders of an insoluble substance, it may be *levigated*.[1] The process of decantation (*elutriation*) is also employed to separate very fine powders, as chalk.

II. PROCESSES OF SEPARATION.

For the separation of the desired ingredients from the inert material three methods are in vogue, depending upon the nature of the active constituents. If volatile constituents are to be separated, this may be readily done by the *application of heat* — distillation and sublimation. If they are not volatile, the separation is usually effected by ex-

[1] Made into a thick paste with water and rubbed between two polished slabs.

posing the drug to the *action of some solvent* in which the desired principles are soluble, and the rest, as far as may be, are insoluble. In certain cases some mechanical means are sufficient, as in the separation of fixed oils from seeds, etc., by *pressure*.

Separation by Means of Heat.— This may be done whenever the substances to be separated have a different boiling-point, and are not themselves destroyed by the necessary degree of heat. The methods used must vary according to whether the fixed or the volatile portion is desired, and, if the latter, according to whether it is liquid or solid.

Desiccation, Torrefaction, Carbonization, Ignition.— With all these, the object is to drive off some volatile constituent from a solid, the fixed residue being the portion desired.

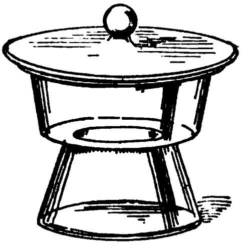

Fig. 29.— Desiccator.

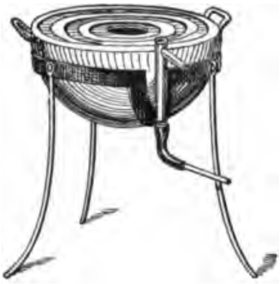

Fig. 30.— Constant level water-bath. (Coblentz.)

When the heat employed is of such degree as not to change the chemic composition, the process is spoken of as *desiccation*. This has been partly discussed on page 44.

For some purposes it is necessary to modify this process. If the last traces of moisture are to be removed, it is necessary to employ heat above that of boiling water, say 110° to 120° C., and the heating must be continued for some time. When such heat is injurious to the substance, the same object may be accomplished by drying in vacuo (p. 48) or by placing the substance in a desiccator (Fig. 29) over some hygroscopic substance — $CaCl_2$, or preferably, concentrated sulphuric acid. A substance or vessel which has been heated and which is to be weighed must always be placed in a desiccator to cool, since moisture is very rapidly attracted from the atmosphere.

Torrefaction.— The process of roasting; the object being to employ such a degree of heat as will alter some of the constituents without affecting others. The roasting of coffee is a familiar example.

Carbonization.— The heating of organic substances under exclusion of air. The object is to destroy the chemic composition without oxidation; carbon results in the process (vegetable or animal charcoal).

Ignition.— This is the process of strongly heating a substance, usually in a crucible, with full access of air, so as to effect complete oxidation; nothing but the ashes remain.

The methods are discussed in text-books on analytic chemistry.

Evaporation consists in vaporizing the solvent from a solution, the object being the concentration of the dissolved substance.

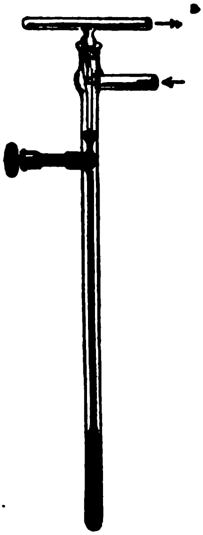

Fig. 31.— Thermo-regulator.

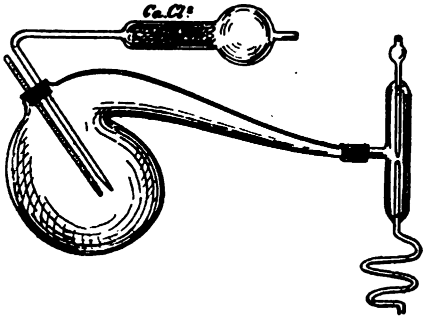

Fig. 32.— Apparatus for evaporation in a vacuum with current of dry air.

Since the rapidity of the evaporation, aside from the quantity of heat applied, depends upon the extent of the liquid exposed to the air and to the heat, dishes as flat as possible are chosen. For ordinary pharmaceutic and chemic purposes, those made of porcelain are of most frequent service. Vessels made of glass, iron, platinum, etc., find application in special cases. The heat may be applied directly, say by means of a Bunsen flame, only a piece of wire gauze or a plate of asbestos or iron being interposed. This method can be used only when there is no danger of injuring the solution by excessive heat, either the substance being incapable of change, or the solvent sufficient in amount so that the temperature cannot rise much beyond its boiling-point. If this is not the case, some method must be used of regulating the amount of heat applied, and this is done by applying the heat indirectly through a bath. This consists of an outer vessel filled with water (steam), oil, sand, or air.

The water and oil baths can only be used for temperatures below the boiling-point of these liquids. This is rather higher for oils, but these possess the disadvantage that irritating vapors arise from them. On the other hand, oil does not evaporate as does water. Water-baths require constant attention to prevent them from drying. Constant level water-baths have been devised to obviate this difficulty. They are constructed either on the principle of Mariotte's bottle, or by passing a continuous stream of water through the outer vessels. (Fig. 30.)

Steam is sometimes used instead of water.

Air- and sand-baths are capable of regulation at any temperature. The latter, however, are frequently used merely for the purpose of moderating and equalizing the heat. Air-baths may be improvised by covering a tin pan with a sheet of iron. A much better method is by means of an oven, which may be covered with asbestos.

For keeping the temperatures of air and water ovens constant, various thermoregulators are used of which figure 31 is an example.

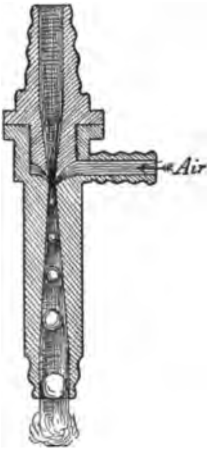

Fig. 33.— Principle of filter-pump.

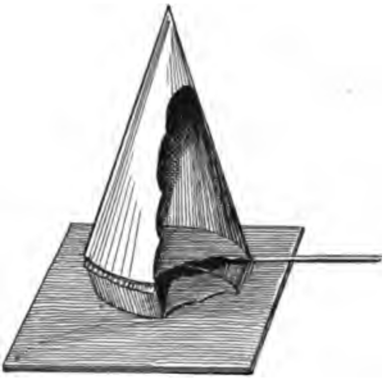

Fig. 34.— Sublimation of benzoic acid. (Coblentz.)

The rapidity of evaporation may be considerably increased by *stirring*, thus exposing a constantly renewed surface to the air. The same object may be secured by creating a current after the manner of a smokestack, by supporting an *inverted funnel* over the evaporating dish.

In cases where the evaporation must be carried on at a temperature below the boiling-point of the solvent, this may be done either by evaporation over H_2SO_4, or in a vacuum, or by passing a current of dried air through the liquid. Figure 32 shows an apparatus for the evaporation of liquid at low temperature, combining vacuum and fine stream of dried air. The tube which carries the air must have a fine capillary opening. Figure 33 shows the principle of the ordinary water filter-pump used to produce the vacuum.

The evaporation which occurs from the surface of a liquid exposed to air at ordinary temperature is called "*surface evaporation.*" It varies in quantity with the amount of surface exposed and with the temperature and dryness of the air.

When very inflammable liquids (ether) are being evaporated, this should be done on a large water-bath, and the Bunsen flame should be protected by wire gauze.

Sublimation.— The process of separating a volatile from a non-volatile solid.

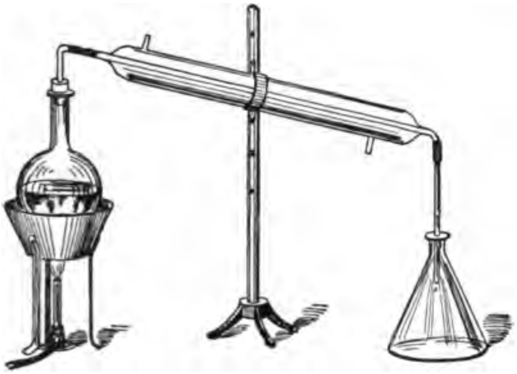

Fig. 35.— Still, Liebig's condenser, and receiver.

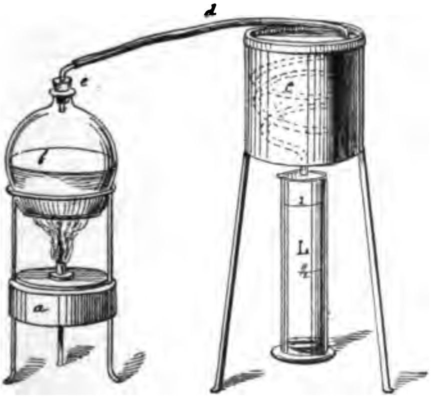

Fig. 36.— Still, worm condenser, and receiver.

(The difference between sublimation and distillation consists in this, that the product is solid in the former, liquid in the latter.)

This may be done in a distilling apparatus, provided that the cooling tube has sufficient lumen to prevent its clogging by the condensation of the sublimate. The apparatus is, however, usually modified. A simple illustration of this process is the old method of manufacturing benzoic acid from gum benzoin, a paper hood being used as condenser. (Fig. 34.)

Distillation.[1]— The typical apparatus used for distillation consists of three parts (Figs. 35 and 36):

---

[1] Although this is such a ready and simple means of separation that one would think that it must have been discovered at a very early time, such does not appear to have been the case. We find the first record of it in the writings of the fourth century alchemists.

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The *still,* the vessel in which the vapor is generated.

The *condenser,* the apparatus in which the vapor is cooled.

The *receiver,* for receiving the condensed product.

The Still.— This consists of either a retort, an alembic, or a flask.

The *retort* is illustrated by figure 37. The bend at *X* should go as far as possible inward, so as to prevent the carrying over of liquid. In filling a retort, care must be used not to get any liquid in the neck. A funnel with a long tube attached must therefore be used. An opening (tubulure) at *a* is convenient for filling and for holding a thermometer.

The *alembic* is the old-time still, and differs from the retort in having a chamber (helm or hood) where the vapor is partly condensed. By fitting the helm on the body with a flange joint a very wide opening can be secured, which is of use in cleaning.

Flasks with perforated corks answer for most purposes. The cork should contain two holes, to allow the introduction of a thermometer. To prevent the projection of liquid into the delivery tube during too violent boiling, the upright limb can be expanded into a bulb.

Liquids in contact with very smooth surfaces — *i. e.,* in glass vessels — may be heated to a temperature considerably above their "boiling-point," when the vapor is suddenly disengaged, and causes "*bumping.*" This may be avoided by introducing some irregular bodies into the flask — glass, zinc, pumicestone, platinum wire, etc., according to the nature of the liquid; or by passing a fine current of air through the liquid.

The Condenser.— The object of this apparatus is to cool and consequently condense the vapors which have been formed in the heated still.

With substances having a very high boiling-point, above 150° C., the air alone may be sufficient to effect condensation. With most substances, however, a constantly renewed layer of cold water is necessary.

The form of condenser which is most used in laboratories on account of its convenience is the *Liebig's* (Fig. 35).

The *worm* offers a larger surface (Fig. 36).

As *receiver,* a common flask or breaker is ordinarily used.[1]

The heating of the retort may be done in any of the ways mentioned under evaporation. With substances which are injured by being heated alone, the distillation is done by a current of steam generated in another vessel.

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[1] It would be without the scope of this treatise to enter into the method of glass-blowing, cork-boring, etc., which are needed in fitting up a still. Such will be found in most elementary text-books on chemistry.

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Fractional distillation is the process of separating a mixture of liquids of different boiling-points by distillation.

This cannot be done with any degree of completeness unless the boiling-points lie far apart. The separation, however, will be the more complete, the more exactly the temperature can be observed and controlled. The thermometer-bulb must be adjusted at the level where the vapors leave the flask. This is facilitated by using "fractional distillation flasks" (Fig. 38).

Destructive distillation is the name applied to the process of heating a substance so strongly as to decompose it, and collecting the volatile products arising from this decomposition: *i. e.*, in the case of organic bodies, tar.

Solution.— This consists of incorporating a solid into a liquid in a state of "molecular subdivision."

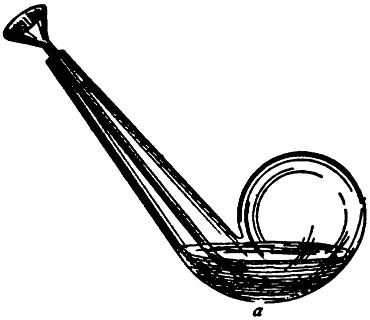

Fig. 37.— Filling a retort.

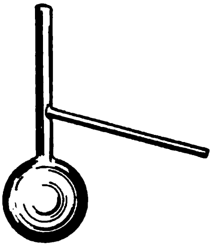

Fig. 38.— Fractional distillation flask.

That is, the molecules of the solid diffuse themselves in the liquid and become so widely separated that no solid particles are by any means discernible. In other words, the solid is liquefied and its molecules intermingle with those of the solvent.

A *simple solution* is one occurring in the manner described, the change in the solid being physical. When a chemic change takes place, the process is called *chemic solution* (such as the solution of a metal in an acid).

A solvent is capable, under given conditions, of dissolving but a limited amount of a given solid. A solution which contains as much of the solid as the liquid can dissolve under these conditions is called a *saturated solution*. The condition which has the greatest influence upon solubility is the temperature. A liquid can usually dissolve the more of the solid, the higher the temperature. There are, however, a few exceptions to this rule.

If a solution saturated at a high temperature is allowed to cool, the originally dissolved substance will be in excess of saturation. Under certain conditions it may still remain in solution at the lower temperature, this being a *supersaturated solution*. Ordinarily, however, the excess will separate, usually in crystalline form. This process is called *crystallization*. It is frequently used as a means of purification.

A solution which contains less of the solid than it is capable of dissolving is an unsaturated solution. A solution which is saturated with one substance is still capable of dissolving others, though not as much as if it were the pure solvent.

Solution is effected by placing the solvent in contact with the substance to be dissolved. The process may be hastened by applying heat, or by exposing the largest possible surface to the action of the solvent. The latter may be done by using the substance in a pulverized condition, and by constant stirring. With *circulatory solution* the substance is suspended near the surface of the solvent. As this takes up the substance, it gains in specific gravity, and hence sinks to the bottom, a new portion of liquid taking its place. (Fig. 39.) The same object may be secured by a process analogous to percolation, the powder being placed in a funnel partly occluded by a pledget of cotton, etc., and the solvent allowed to percolate through it.

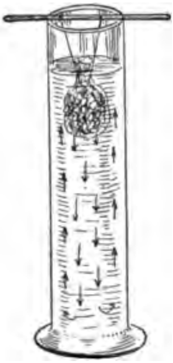

FIG. 39.—Circulatory solution.

The simple solution of a substance always causes a depression of temperature. But if a chemic change occurs, the temperature may be raised.

The process of solution applied to crude drugs has for its purpose the separation of the active ingredients from the insoluble inert material. The object is to dissolve out the greatest possible amount with the least possible menstruum. This accomplishes two results: We obtain a strong extract, and we waste neither drug nor menstruum. There are a number of methods of accomplishing this, each with its advocates. They are combinations of two extremes: maceration and percolation. Neither of these is commonly used alone in this country, the practice being to combine the two.

Maceration is by far the simpler process. It consists in simply leaving the solvent in contact with the drug under suitable conditions for a sufficient length of time.

When maceration alone is employed, a given quantity of the drug is put in a bottle or other suitable vessel with a definite proportion of the solvent (called menstruum) and left a certain time, usually two weeks. The liquid is then strained off, the residue (marc) is expressed and the mixed extract filtered. The details of the process are influenced by several considerations:

(*a*) The degree of comminution of the drug: The finer the drug, the less time will be required, and sometimes it is impossible to get thorough penetration unless the drug is powdered.

A coarse powder gives a cleaner solution.

(*b*) Temperature: The solution is the quicker, the higher the temperature. Different names are given to the process according to the temperature at which it is carried out. Maceration proper = room temperature; 30° to 40° C. = digestion; boiling = decoction. Possible injury to some constituents by heat, or evaporation of a constituent or of the solvent, are objections to the application of heat in certain cases.

(*c*) Time: the longer the better.

(*d*) Menstruum. This must be adapted to the drug.

This process of maceration is the one almost exclusively employed in Europe; and it offers certain advantages, not the least being its simplicity and the constant results which it gives. Its main disadvantages are the required time and the loss of the extract retained in the insoluble residue or "*marc*." Certain drugs are physically unfit for percolation, since the moistening causes them to form into a tough mass, as good as impenetrable to the solvent.

The loss of menstruum does not, of course, weigh when an aqueous solvent is used and only small quantities are prepared. Hence maceration is used in making infusions and decoctions.

Infusions are made by pouring boiling water upon the drug (in coarse powder), letting it stand for half an hour, and straining. The usual proportion is 1 : 20. In *decoctions,* the drug is boiled for a quarter of an hour in a covered vessel with water (1 : 20), allowed to cool, strained, and diluted to 20. These preparations do not keep. To secure preservation, acetic acid, glycerin, sugar, or, most commonly, alcohol is added.[1]

Percolation consists in passing a solvent through a thick layer of the powder to be exhausted. This exposes a large surface of the latter; the nearly saturated solvent flows off and fresh unsaturated portions continuously replace it, insuring very rapid solution.[2]

The principle of the method is to pack the powder into a tall vessel, with an opening at the bottom, and to let the solvent trickle through it. Usually the process is combined with a short previous maceration.

The details are as follows:

The powder (the fineness of which depends upon the nature of the drug and is directed for each case by the Pharmacopœia) is moistened in a jar with some of the menstruum. This moistening is for the purpose of swelling the drug, for if this took place in the percolator, the drug would become so firmly impacted that the menstruum could not penetrate through it; or it could even burst the percolator. The moistened powder is then passed through a coarse sieve and transferred to the prepared percolator, which it should fill about two-thirds.

The choice of the shape of the percolator depends upon the nature of the drug. Should the drugs have a tendency to swell, particularly if they are in fine powder or if weak alcohol menstruum is used, a conical percolator is employed: otherwise, the cylindrical. The size corresponds to the quantity of the powder.

---

[1] The amount of preservative which must be added to a preparation to insure its keeping qualities must vary with its nature, and in the same direction as the amount of "extractive." The proportions generally necessary are: Alcohol, 20 to 25%; glycerin, 10%; sugar, 66 Gm. to 100 c. c. of finished product. Alcohol, 20% + glycerin, 5%.

[2] The U. S. Pharmacopœia defines percolation as consisting in "subjecting a substance or a mixture of substances, in powder, contained in a vessel called a percolator, to the solvent action of successive portions of a certain menstruum, in such a manner that the liquid, as it traverses the powder in its descent to the receiver, shall be charged with the soluble portion of it, and pass from the percolator free from insoluble matter."

The percolator is prepared in the following manner (Fig. 40): Into the small end there is inserted a cork perforated by a short glass tube which projects about 1 cm. inside the percolator. The outer end of this tube is attached to a piece of rubber tubing, about one-fourth longer than the percolator, and this to a U-shaped glass tube. This is held to the percolator by a rubber band in such a way that it can be raised and lowered. The percolator is then set in the stand. A pledget of absorbent cotton is loosely packed in the neck of the percolator, and this is covered by a layer of clean sand, and over this goes a well-fitting disk of filter-paper. Then the moistened drug is pressed in — and this is the part of the process which requires the greatest skill and judgment, and on it depends the success of the product. It should be done very evenly, else the menstruum will choose the path of least resistance and some portions of the powder will be entirely exhausted whilst others are still scarcely affected. The firmness of the packing is also of great importance; if not firm enough, the menstruum will run through too rapidly and the percolate will consequently be weak. If too firm, it can not run at all; and if any swelling occurs, the percolator will be broken. Drugs in coarse powder should be packed more firmly than fine powders. An alcoholic menstruum requires firmer packing than a watery one.

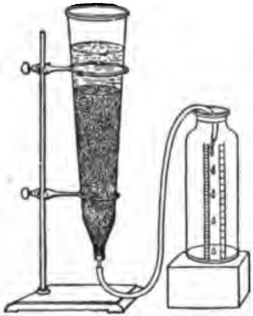

Fig. 40.— Method of percolation (Thornton).

The packing being completed, the menstruum is poured on until it stands an inch or two above the drug; the percolator is then covered and set aside for maceration for a specified time, the tube being raised so that no liquid flows out. When the time of maceration is completed, the tube is lowered and fixed at such a level that the outflow occurs at the rate of 2 to 15 drops per minute. New menstruum is poured on in the measure that the old flows out. Care should be taken to always maintain the layer of liquid above the powder; else cracks may appear in the latter, necessitating repacking.

The process is continued, in the case of tinctures, until a certain volume of percolate is obtained. The quality of the percolate will, of course, depend upon the care and skill of the operator, and the product is apt to vary. Maceration would, therefore, be a better process for tinctures.

This difficulty is avoided in the case of extracts, for here the percolation is continued "until the drug is exhausted"; *i. e.,* until the active ingredients have become completely dissolved out. This is recognized by testing the last portions of the percolate in the appropriate manner, such as Mayer's reagent for alkaloids, water for resins, etc. It may here be remarked that a drug is usually more rapidly exhausted of its active ingredients than of its coloring-matter, so that the last portions of percolate may be colored and yet devoid of activity.

The choice of a menstruum must be determined by the nature of the constituents. The object is, to extract all the active ingredients and the minimum of inactive. Alkaloids and resins require strong alcohol; gums, weak alcohol; licorice, alkaline alcohol; sanguinaria and ergot, acidified alcohol; gentian and quassia, water plus alcohol enough to keep.

The *most useful pharmaceutic solvents* are the following:

Water or Glycerin.— Dissolves salts (including those of alkaloids), sugar, gums, tannin, acids, and alkalies, etc.

Dilute Acetic Acid.— Especially for alkaloids.

Alcohol.— Dissolves alkaloidal salts, neutral principles, resins, volatile oils. Precipitates gums and most inorganic salts.

Ether, Chloroform, Acetone.— Dissolve free alkaloids, neutral principles, resins, volatile and fixed oils, and fats.

Petroleum Benzin.— Solvent properties as the preceding, except resins.

Aromatic Spirits of Ammonia.— Dissolves resins and organic acids.

In the case of *very volatile menstrua,* such as ether, chloroform, or petroleum ether, some means must be employed to collect and return the evaporated solvent. One of the best apparatus of this kind is that of Soxhlet (Fig. 41).

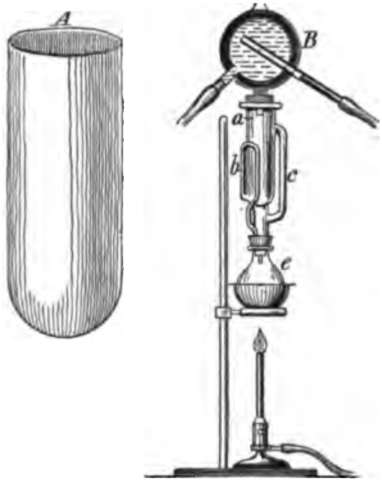

Fig. 41.— Soxhlet extractor: A, cartridge of filter paper, for holding the powder; B, the entire apparatus, mounted, connected with a flask (e) and a "ball" condenser.

Expression.—The process of separating a liquid from a solid by pressure.

Its principal employment in pharmacy is for the recovery of tinctures from the "marc" *i. e.,* the liquid retained by the drug residue after maceration and percolation. It is also a process of separating fixed oils.

The drug is put in a coarse strong cloth and subjected to pressure in a press. These are of various patterns: screw, lever, hydraulic, or centrifugal. The pressure must be applied gradually to prevent the bursting of the cloth. Small quantities can often be pressed sufficiently by putting them into a cloth and tightly twisting the end.

Straining or **Colation.**— The process of separating solid coarse particles from a liquid by pouring it through a cloth or strainer.

Filtration.— The process of separating solid particles (fine or coarse) from a liquid by pouring it through a finely porous material, such as filter-paper.

The usual material for filtration is pure unsized paper, "filter-paper," which is made of various grades,— white and gray,— and of varying texture and thickness according to the purpose for which it is to be used.

There are two principal methods of folding a filter — plain and plaited (see Exercise 7).

These two filters have different uses. The plaited filter offers a much larger surface for filtration and is therefore more rapid; it is the form usually employed in pharmacy. The plain filter, on the other hand, facilitates washing and removal of the precipitate, and is of more frequent use in chemistry.

The creases should not be carried sharply to the point, but should be quite light ¼ to ½ inch from the end, to prevent breaking.

The liquid should be poured in cautiously, so as to fall about the outer third of the surface of the liquid: if poured at the center, the momentum is apt to break the point of the filter; if poured too near the edge, it is apt to get outside.

Filtration may often be hastened by the use of a vacuum apparatus. (Fig. 33, p. 48.)

Other materials are sometimes employed instead of paper. A very useful filter for large quantities of liquid is made from felt. A plug of glass-wool or asbestos placed in the tube of the funnel is especially useful for strong acids or alkalies. A cell of porous clay is also employed, as in the various forms of the Chamberland filter. With this a vacuum is indispensable.

Another process of frequent use in the separation of crystalloids from colloids is *dialysis.*

When water is added to an aqueous solution of any substance, the dissolved molecules will tend to distribute themselves evenly throughout the liquid. This diffusion will occur, in the case of crystalloids, even when the solution is separated from the water by a parchment membrane. In other words, the crystalloid molecules pass freely through the pores of the membrane under the given conditions. Colloids, such as proteids, gums, gelatin, etc., on the other hand, do not pass through, so that this gives a method for separating these two classes of substances. The most useful form of dialyzer is furnished by a parchment tube containing the solution and suspended in a vessel of water.

Decolorization.— It is often desirable to remove the coloring-matter from a solution. This may sometimes be accomplished by choosing appropriate solvents. More often, however, the solution is filtered through recently calcined animal charcoal. This very often retains some of the active constituents as well as the coloring-matter.

Clarification.— The process of rendering turbid mixtures clear and transparent, by removing the suspended solid. When filtration does not suffice, the object is accomplished by agitating the mixture with insoluble powders (talcum, phosphate of lime, aluminum hydrate) or by adding egg-albumen and boiling; or sometimes by the centrifugal machine.

CHAPTER IV.

(A) SPECIAL PHARMACEUTIC PREPARATIONS.[1]

The Pharmacopœia divides its preparations into certain definite classes, established by long usage, such as Waters, Spirits Tinctures, Extracts, Pills, Plasters, Ointments, etc.

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[1] Exercises 6 and 7.

This classification will be retained. The classes will be discussed as regards their definition; reason of existence; some general notion of the manner of preparation; the strength of their most important members.

For convenience of study, it is customary to combine these classes into larger groups. In doing so we shall not bind ourselves to any definite or arbitrary scheme, but shall use now one, now another character, as they may seem important.

Liquids may be classified by the nature of the solvent whether aqueous, alcoholic, or other.

TABLE III.—SCHEMA OF SOLUTIONS AND EXTRACTS.[1]

1. SOLUTIONS PROPER.—	(a) *Aqueous:*	Aquæ. Liquores. Mucilagines.	
	(b) *Alcoholic:*	Spiritus.	
	(c) *Other menstrua:*	Glycerita (Glycerina, B. P.). Oleata. Collodia.	
2. EXTRACTS (solid as well as liquid).—	(a) *Aqueous:*	Infusa. Decocta.	
	(b) *Alcoholic:*	Tincturæ. Succi. Liquores concentrati (B. P.). Fluidextracta (Extracta liquida, B. P.). Extracta. Abstracta. Resina.	
	(c) *Other menstrua:*	Syrupi. Elixiria. Mellita. Oxymellita (B. P.). Confectiones (solid).	(Saccharine.)
	Here may be inserted:	Aceta (vinegar). Oleoresina (acetone). Vina (wine).	

WATERY SOLUTIONS.

Their advantage lies in the fact that water is a cheap solvent of very wide applicability, itself devoid of any therapeutic property. In the case of substances which are insoluble in it, it cannot of course be employed. The greatest drawback lies in the fact that watery solutions of organic substances do not keep. If the quantity of organic matter is small, fungoid growths develop; if large and proteids are present, infusoria are also frequent. Solutions of chemic substances are less subject to this change, as they do not furnish a pabulum, and are often themselves antiseptic.

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[1] The student should learn to distinguish clearly between these preparations, according to the definitions given below.

1. **Aquæ** *(Waters)*.— Clear aqueous solutions of volatile substances. Two very dissimilar classes of preparations come under this heading:

(*a*) *Flavored Waters.*— Extremely weak but saturated solutions of almost insoluble organic substances, for the most part essential oils. These are alone included under Aquæ in the B. P.

The quantity of active substance in them is just large enough to give them a pleasant flavor without imparting to them any noticeable therapeutic properties. The absence of alcohol makes them good solvents for salts, which are generally insoluble in this liquid. Hence their main use is as a pleasant vehicle (a vehicle being the substance which serves for the conveyance of another substance). Dose practically ad libitum.

(*b*) *Solutions of Chemic Gases.*— Strong and with distinct therapeutic properties. Their dose is usually a few drops. (In the British Pharmacopœia these come under the heading of Liquores).

Preparation of first class: These are prepared either by distillation or by trituration; Aq. Creosoti and Chloroformi by shaking.

In the method of trituration, the object is to distribute the oil as finely as possible, by the intervention of some inert and insoluble foreign substance, so as to facilitate solution. Talcum or shredded filter-paper may be used for this purpose. They may also be prepared by shaking with hot water or by distillation. The preparation of Aqua Menthæ Piperitæ exemplifies the typical U. S. P. method: Triturate 2 c.c. of oil of peppermint with 15 Gm. of purified talc, gradually add 1,000 c.c. of distilled water with continued trituration, filter, and pass the filtrate through the filter repeatedly until the Peppermint Water is perfectly clear.

Waters, as a rule, do not keep well. Their keeping qualities may be improved by adding to them some of the oil of which they are solutions. This floats on the surface, and in this way excludes air and bacteria, and at the same time insures permanent saturation.

Preparation of Second Class.— The second class is prepared by passing the gas through water. The quantity of dissolved gas is then tested by chemic assaying and the solution standardized.

The U. S. P. recognizes three waters[1] of this class (Ammoniæ, Ammon. fortior, and Hydrogenii Dioxidi); and ten flavored waters. The total number of official waters is 17. Aq. Hamamelidis (Witchhazel) contains some alcohol. Aq. Camphoræ, Chloroformi, and Creosoti have therapeutic properties.

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[1] These figures are given to indicate the relative importance of the class. Unless otherwise stated, they refer to the U. S. P.

2. Liquores.— Aqueous solutions of solid chemic salts or hydrates, made either by directly dissolving the pure salt in water by trituration or heat; or, more often, by chemic decomposition (simple and chemic solution). (The British Pharmacopœia includes solution of gases and alcoholic solution of fixed substances under this heading).

Many have *antiquated names:*

Spirit. Mindererus = Liquor Ammonii Acetatis.
Donovan's Solution = " Arsenii et Hydrargyri Iodidi.
Lugol's Solution = " Iodi Compositus.
Lead Water = " Plumbi Subacetatis.
Goulard's Extract = " " " Dilutus.
Water Glass = " Sodii Silicatis.
Basham's Mixture = " Ferri et Ammonii Acetatis.
Monsel's Solution = " Ferri Subsulphatis.
Effervescent Magnesia = " Magnesii Citratis.
Fowler's Solution = " Potassii Arsenitis.
Labarraque's Solution = " Sodæ Chlorinatæ.

Their use consists mainly in the convenience of measuring the relatively large volumes of the solution against weighing the small quantity of salt. Water is chosen as the solvent because salts are but little soluble in alcohol, and because the therapeutic qualities of the latter are not desired.

Solutions, when used for special purposes, receive special names, thus: Injectiones (Hypodermicæ; Urethrales), Collyria (Eyewaters), Lotiones (Washes), Gargarismæ (Gargles), etc.

The U. S. P. contains 25 Liquores. The *strength* of the following is important:

U. S. P.— All liquors containing arsenic, 1%; Liq. Ferri Chloridi, nearly 29% Fe_2Cl_6; Liq. Plumbi Subacetatis, 25%; Liq. Plumb. Subac. Dil. ¾%; Liq. Iodi Comp., Liq. Potassii Hydroxidi, and Liq. Sod. Hydrox, 5%.

B. P.— All liquors containing arsenic, 1%; Liq. Ferri Perchloridi, 6% Fe; Liq. Fer. Perchlor. Fortis, 22½% Fe; Liq. Iodi Fortis, 14%; Liq. Plumbi Subac. Fortis, 25%; Dilutus, ⅓%; Liq. Potass. or Sodæ, 5%; Liq. Atropinæ Sulph., Liq. Morph. Acet. or Hydrochloratis, and Liq. Strychn. Hydrochlor., 1%.

Injectiones Hypodermicæ (B.P.) are strong watery solutions of active drugs, intended for subcutaneous administration. They are sometimes preserved sterile by the addition of carbolic or salicylic acid. *Dose,* to 10 min. (B.P.).

The following are official (B.P.):

Injectio Apomorphinæ Hypodermica, 1%.
Injectio Cocainæ Hypodermica, 10%.
Injectio Ergotæ Hyp., 30% of extract.
Injectio Morphinæ Hyp., 1% of tartrate.

3. Mucilagines.— Aqueous solutions of gummy substances. Four are official.

Since gums are insoluble in alcohol, mucilages are incompatible with this substance. They should be recently prepared because they are very apt to mold. They are made by either hot or cold process: the former being solution by heat, the latter by percolation. Heat should be used only when necessary (tragacanth), as it usually causes discoloration of the product.

ALCOHOLIC SOLUTIONS.

Alcohol is a specific solvent of certain substances (volatile oils, alkaloids, resins). In prescribing, avoid mixing these with an aqueous solution.

Further, alcohol is a good preservative; but it has distinct therapeutic qualities, which may or may not be useful.

4. Spirits.— Alcoholic solutions of volatile drugs. They are all fairly strong. Twenty are official, eight of these being used solely as flavors.

As in Aquæ we have, as to **preparation:** *Simple solution; distillation* (liqueurs and strong "liquors"); *chemic decomposition* (spiritus ætheris nitrosi).

5. Glycerita (Glycerina, B.P.).— Solutions in glycerin. Glycerin has good solvent power for many substances. It keeps well, and is useful especially for external application on account of its adhesiveness. Glycerin is also less irritant than alcohol and devoid of the pharmacologic action of the latter agent. Six glycerites are official.

6. Oleata.— Solutions of bases (metallic or alkaloidal) in oleic acid. They are not definite chemic compounds, as the name would imply. The rationale of their use is, that a substance is not absorbed by skin from aqueous, but from oily solutions. Many substances, again, are not soluble in oils, but dissolve in oleic acid. The oleates, therefore, constitute a useful class of preparations when it is desired to secure the absorption of a drug through the skin. Many are diluted with olive oil. Five are official — four being oleates of alkaloids, the fifth of mercury.

7. Collodia.— Solutions of gun-cotton in ethereal fluids. By the evaporation of the solvent they form a film on the skin, and thus act like plasters. Collodia must not be brought near fire. Five are official.

The base is collodion: This is made by dissolving pyroxylin, 4 parts, in a mixture of 75 parts of ether and 25 parts of alcohol.

Pyroxylin is prepared by the action of HNO_3 on cellulose (cotton) in the presence of H_2SO_4. This may result in a number of substitution products, of which tetranitrocellulose, $C_{12}H_{16}(ONO_2)_4O_6$, is official. Hexacellulose is the explosive.

SOLUTIONS MADE BY EXTRACTION.

8. Infusions.— Aqueous solutions of the soluble principles of vegetable drugs, obtained by brief maceration in hot or cold water.

9. Decoctions.— Infusions in which the ingredients have been boiled with water for at least fifteen minutes.

Infusions and decoctions are especially useful when it is wished to extract some principle which is more soluble in water, or when the therapeutic effect of alcohol or the mechanical incompatibility of alcohol with salts is to be avoided. There are some inconveniences connected with their use: They take a long time to prepare. Like all watery solutions, they spoil quickly, and must, therefore, be made fresh. The decoction can only be used if there are no delicate constituents to be destroyed by boiling.

The solvent being so very cheap and having no action, it is usual to make decoctions considerably weaker than tinctures. In prescribing infusions or decoctions of potent drugs, the proportion should always be stated by the prescriber.

When not specified, the strength should be 5%, and the process as follows:

Infusa.— 1,000 c. c. of boiling water are poured on 50 Gm. of the coarsely comminuted substance, the vessel is covered tightly, and allowed to stand for half an hour in a warm place. It is then strained with expression, and enough water is poured through the strainer to make the infusion measure 1,000 c. c.

Decocta.— 50 Gm. of the coarsely comminuted substance and 1,000 c. c. of cold water are boiled in a covered vessel for 15 minutes, cooled to about 40° C., strained and expressed, and cold water added through the strainer to make the decoction measure 1,000 c. c.

Three infusions are official (Infusum Digitalis, Pruni Virginianæ, and Sennæ Compositum). These are all exceptions to the 5% rule. The U. S. P. does not name any decoctions. The dose of non-poisonous infusions and decoctions lies between 15 and 120 c. c. (½ to 4 ozs.).

10. Tincturæ.—Alcoholic or partly alcoholic solutions of the useful constituents of such drugs as are not wholly soluble in the menstruum.

Exceptions to this definition are tincture of iodin, tincture of chlorid of iron, and tincture of tolu, in which the solution is complete.

Sixty-six tinctures are official. They are all weaker than fluidextracts, their *strength* varying from 0.4% to 50%. Until the last revision of the U. S. P., the strength of the tinctures was quite arbitrary. In conformity with the recommendation of the "Conférence Internationale pour l'Unification de la Formule des Médicaments Héroiques," held in Brussels in September, 1902, the strength of all potent tinctures has been placed at 10%. This should be remembered especially for Tr. Aconiti and Tr. Veratri. The other tinctures have also for the most part been adjusted to either 10% or 20%: 25 of the official tinctures have a strength of 10%; 26 of 20%; a few unimportant of 50% and 5%. The important exceptions are: Tr. Ferri Chlor., 13.28%; Iodi, 7%; Opii Camphor., 0.4%.

The tinctures are in many respects the most useful therapeutic preparations: The dose is relatively large and uniform (about 4 c. c. for the non-toxic); the quantity of solvent is sufficiently large to keep the principles in solution; the use of heat in the preparation is avoided.

The greater number of tinctures are prepared by percolation; a few by maceration. The menstruum is alcohol or alcohol and water; glycerin is added in a few cases; Tr. Sanguinariæ contains some acetic acid. Aromatic Spirits of Ammonia is used in the *ammoniated tinctures* (Tr. Guaiaci Amm. and Tr. Valerian Amm. being official).

The manufacture of tinctures is illustrated by *Tinctura Digitalis:* Moisten 100 Gm. of Digitalis in No. 60 powder with 40 c. c. of Diluted Alcohol, transfer it to a percolator, and, without pressing the powder, allow it to stand, well covered, for 6 hours; then pack it firmly and pour on enough Diluted Alcohol to saturate the powder and leave a stratum above it. When the liquid begins to drop from the percolator, close the lower orifice, and, having closely covered the percolator, macerate for 24 hours. Then allow the percolation to proceed slowly, pouring on sufficient menstruum to obtain 1,000 c. c. of Tincture.

Detannated Tinctures are tinctures from which the tannin has been removed (as by powdered skin). They do not precipitate with iron salts.

Ethereal Tinctures are made with ethereal spirit, a mixture of seven parts of ether and three parts of alcohol.

Since some drugs are supposed to lose part of their activity by drying and keeping, a class of tinctures made from the freshly collected green drugs has been introduced under the name of *Tincturæ Herbarum Recentium.* These preparations are not at all popular; in fact, almost unused and justly so. They are of very inconstant strength, since the natural moisture of plants is variable. Again, they can only be prepared in the localities where the plants are native and where there often are no reliable facilities for their manufacture. These remarks apply equally to *Succi* of the British Pharmacopœia, made by using one part alcohol and three parts of the freshly expressed juice.

The directions of the U. S. P. are to macerate 500 Gm. of the fresh herb with 1,000 c. c. of alcohol for fourteen days, to express and filter.

11. Wines are tinctures in which wines have been substituted for alcohol. They have a more pleasant taste, but inferior keeping qualities.

Ten vina are official, including plain white and red wine. The medicated wines are generally mixtures of fluid extracts with white wine; sufficient alcohol being added to insure preservation. Vin. Cocæ is prepared with red wine. The potent wines contain 10% of the drug, like the tinctures.

Aceta are medicated vinegars, prepared by maceration with dilute acetic acid. Two are official, Opii and Scillæ. Both contain 10%.

12. Fluidextracta (fluidextracts, U.S.P.; liquid extracts. B.P.) may be defined as fluid alcoholic or acetic preparations of vegetable drugs, of such strength that 1 c.c. contains the active ingredients of 1 Gm. of the drug.

Eighty-five of these fluidextracts are official. They are the most concentrated fluid preparations, with the consequent advantage of small dosage. Their uniform strength is chiefly of pharmaceutic importance.[1]

On the other hand, the heat which must necessarily be used in their preparation is never beneficial. On account of their concentration, precipitates are apt to form on standing, and while these are often inactive, they may contain the active principles. They are also much more subject to precipitation on mixture with other liquids, and the dose is usually so small that they require some such admixture.

Fluidextracts are prepared by percolation, the first four-fifth of the percolate being set aside, the remainder evaporated to the consistency of a soft extract, dissolved in the reserved portion, and menstruum added to make the required volume.

Fluidextractum Aconiti is typical: mix 750 c. c. of Alcohol with 250 c. c. of Water. Moisten 1,000 Gm. of Aconite in No. 60 powder with 400 c. c. of the mixture, pack firmly in cylindrical percolator; proceed as usual (see Tinctures), macerating for 48 hours, then percolating slowly, until the Aconite is exhausted.

Reserve the first 800 c. c. of the percolate, and evaporate the remainder, in a porcelain dish, at a temperature not exceeding 50° C., to a soft extract; dissolve this in the reserved portion, mixing thoroughly. Assay the preparation and add enough menstruum so that 1 c. c. of the finished fluidextract contains 0.004 Gm. of aconitin, corresponding to 1 Gm. of Aconite.

The menstrua of fluidextracts of Lobelia, Sanguinaria, and Scilla consist of diluted acetic acid. All other fluidextracts are prepared with alcohol or alcohol and water, sometimes with the addition of glycerin. Conium, Ergot, and Nux Vomica contain a small amount of acetic acid; Senega some pot. hydroxid; Taraxacum some sod. hydroxid; and Glycyrrhiza some ammonia.

Liquores concentrati (B. P.) are more concentrated than the tinctures, but weaker than fluidextracts.

13. Extracta, *solid extracts,* must not be confused with the fluidextracts. They are solid or semisolid preparations obtained by evaporation of solutions of the medicinal principles of drugs.

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[1] The practice of preparing tinctures, infusions, &c., by the dilution of the fluidextracts is highly reprehensible, since these dilutions often differ materially from the orthodox preparations.

Twenty-eight of these are official. They are convenient for administration in solid form, *e. g.*, in pills, ointments, plasters, etc. All the potent, and most of the other, extracts are adjusted to four times the strength of the fluidextracts, with the following important exceptions: Ext. Opii, twice; Ergotæ, eight times; Physostigmatis, 13 times, the strength of fluidextracts.

Some of the solid extracts are dry, others of a "pilular" consistency, *i. e.*, like a pill-mass. Ext. Malti is of the consistency of thick honey. Most extracts are prepared by percolating and subsequent evaporation; the last and weaker portions of the percolate being evaporated first, to avoid the deleterious actions of prolonged heat on the main portion. Some of the extracts are obtained by evaporating the fluidextract. The menstruum is sometimes water, or alcohol, or a mixture of both; acetic acid being added in some cases. The finished product is assayed, if possible, and adjusted to a definite standard by the addition of sugar of milk.

Abstracts, now obsolete, were adjusted so that 1 Gm. equalled 2 Gms. of drug.

Inspissated Juices (extractum viride, B. P.) are obtained by evaporating the expressed juice of the fresh plant. They are unimportant.

Artificial resins are precipitates obtained by mixing alcoholic solutions with water. Where they constitute the active principle, this is a convenient method of isolating it in a concentrated although somewhat impure form. Their strength is fairly constant. They are practically identical with the eclectic "resinoids." Three are official (Resina Jalapi, Podophylli, Scammonia).

Oleoresina are extracts containing the resinous and oily constituents of the drug. Six are official. Five of these are obtained by evaporation of the acetone percolate. Oleores. Cubebæ is made with alcohol.

14. Syrups are dense saccharine solutions of medicinal substances.

Simple syrup is practically a saturated solution, and contains 85 Gm. of cane-sugar in 100 c.c. Syrups are usually prepared by first making an infusion, and dissolving in this the sugar, either by heat or by percolation, according to whether or not the drug is injured by a high temperature. In special cases modifications may be introduced. *Honey* is sometimes used instead of cane-sugar, making a class of preparations called *mellita.* If acetic acid is added to this, we have *oxymellita.* Twenty-five syrups and one flavored honey are official. Some syrups are prepared by mixing the fluidextract and syrup.

15. Elixirs are aromatic, sweetened spirits, which may be medicated.

They are very useful, since they combine the solvent properties of alcohol and of water, and are very agreeable to the taste. The most useful and best "aromatic elixir" is flavored with orange peel, lemon, coriander, and anise. Three elixirs are official; two of these are vehicles — Aromatic Elixir and El. Adjuvans. The latter consists of aromatic elixir and fluidext. glycyrrhiza. They contain about 25% of alcohol.

Confections are thick medicated jams.

They were formerly very popular, but have now been almost abandoned. *Electuaries* were similar but somewhat thinner preparations.

16. Mixtures, in the wider meaning of the word, are fluids resulting from the mixture of fluids with other fluids or with solids. They comprise: Linimenta, Misturæ, Emulsa.

If they are intended for external application as counter-irritants, they are called **liniments.** Eight of these are official.

Mixtures, in the narrow meaning of the term, are generally suspensions of a solid in a liquid, sometimes by the use of a gummy substance; for heavy powders cannot be evenly distributed in a light liquid without this aid. Four are official.

17. Emulsions are mixtures of a milky appearance, made by suspending fats, oils, or resinous substances in aqueous liquids by the intervention of some viscid, usually gummy, substance.

The object of emulsification is to break up the insoluble oil into the finest particles and to envelop each of these in a coating of the emulsifying agent, which will keep them from reuniting. This allows of dilution, of the admixture of other substances, and it facilitates absorption. Milk is a natural emulsion in which the butter-fat is kept in emulsion by the casein. It may be taken as a type to which artificial emulsions must conform. The globules must be uniform and of about the same size as those in milk.

Emulsions may be divided into the following classes:

1. Natural emulsions, such as are found ready formed in nature. Instances of these are milk, the yolk of egg, and some plant juices.

2. Gum-resin and seed emulsions; that is, emulsions made from such substances as contain their own emulsifier. Examples of such gum-resins are ammoniac, asafetida, and myrrh. The undried drugs should be used in making these emulsions, since they are largely spoiled by drying. The drugs are reduced to a coarse powder and water is added gradually. Seeds which yield such emulsions are poppy, hemp, and almond.

3. In artificial emulsions an emulsifier must be added. Quite a number of substances may be used for this purpose, the principal ones being gum acacia, tragacanth, yolk of egg, Irish moss, soap bark, and extract of malt. The substance most commonly used is gum acacia. This emulsifier is incompatible with large quantities of alcohol, borax, tincture of iron, or glycerin. It may be used by either the Continental method, in which a nucleus is first formed from gum, oil, and water, and to which the remainder of the water may then be added; or by the English method, in which a mucilage is first made, to which the oil and water are added in alternate small portions. The *Continental method* deserves the preference. To form a nucleus there should be used for each part of oil one-fourth to one-half part of acacia and one part of water. Stir the oil with the acacia in granular powder, then add the water at once. The mixture of the oil and the gum must not be allowed to stand too long before adding the water, otherwise it will cake. In the *English method* the acacia, the amount of which should be half that of the oil, is rubbed up with an equal volume of water and then small portions of oil and water are added alternately. If this addition should be done too rapidly, there is danger that the emulsion will separate or "crack." This does not necessarily spoil it, for it may be re-emulsionized by adding it to a fresh portion of acacia and repeating the process.

In making medicated emulsions the ingredients should be mixed in the following order: First the nucleus, then the flavoring, then the syrup, and, lastly, the water in which the solids have been dissolved.

In *yolk emulsions,* the yolk of egg is used in place of the nucleus in the Continental method. The yolk is triturated in a mortar and the oil and water are added alternately in small portions. One yolk suffices for from one to two ounces of oil. The yolk emulsions are incompatible with the same substances as gum emulsions and do not keep nearly as well.

Soap bark has saponin for its emulsifying agent. It is not incompatible with any of the above-named substances, but possesses very decided therapeutic properties, which preclude its use in many cases. It is used in the proportion of 1 part of the tincture to 8 parts of the oil: Place the tincture in a dry bottle, add the oil in portions, and shake after each addition. Finally add the water. Crude saponin (0.3 : 100 of oil) can also be employed.

Extract of malt emulsifies its own weight of oil. It is used as the nucleus in the Continental method.

Solutions of alkalies may also be used for emulsification, since they form soaps, but they are usually not desirable.

Six emulsions are official: one seed (Amygdalæ); one gumresin (Asafœtidæ), and four artificial. These are made by the Continental method. Thin liquids, which do not emulsify readily, are thickened by the addition of expressed almond oil.

SOLID PREPARATIONS.

18. Powders are finely powdered drugs intended for either external or internal administration.

When intended for external use, as for dusting-powders, extreme fineness is the main desideratum. They should in this case be mixed with a spatula and not in a mortar, since the former insures greater smoothness. When intended for internal use, they are generally folded in papers (*chartulæ*). It must be borne in mind that hygroscopic (deliquescent) substances, such as potassium acetate or citrate, cannot be prescribed as powders, nor such substances as become a fluid when mixed (*e. g.*, camphor and chloral). In making compound powders, one should begin with the smallest ingredient and add the others in the order of their amount, triturating thoroughly after each addition. In dividing the powder, it is not usually necessary to weigh out each powder. The object is generally accomplished with sufficient accuracy by flattening the powder on a piece of paper, squaring off the edges, and dividing into a number of equal parts by means of a spatula. In the case of more bulky powders, such as Seidlitz powders, measures are used. Nine powders are official. These are all mixtures.

Granular Effervescing Salts.— These are a pleasant form of administering many salts, the CO_2 helping to disguise the taste, and favoring absorption and peristalsis. The basis is a mixture of sodium bicarbonate and tartaric acid or citric acid; to these is added the medicinal agent and sugar enough to make the dose a teaspoonful. This mixture is softened by heat or moistened with alcohol, well stirred until solid, and pressed through a sieve. They are dissolved in half a glass of water just before taking. A number of these preparations are official.

Triturations are powders obtained by triturating the active substances with some inert material such as sugar of milk.

Their advantage lies in the greater ease in weighing out a comparatively large amount of substance. When no special directions are given, triturations are made of a strength of 10%. The trituration of elaterin is the only one official.

Eleosacchara are triturations of volatile oils with sugar in the proportion of 1 : 30. They are used for the purpose of flavoring other powders.

To get a definite dose and to reduce the bulk of the substances when it is desired to administer them in dry form, and when the inconvenience of powders is to be avoided, we employ lozenges, triturates, pills with various coatings, capsules, wafers, or cachets. The administration of substances in dry form always delays their absorption, and this is especially the case if the preparations are coated. On the other hand, they have the advantage of reaching the intestinal canal with little change. One must always be careful not to prescribe pills, etc., of such bulk that they cannot be swallowed.

19. Pills may be defined as spherical or elongated masses of medicinal substances, of such size as to be convenient for swallowing; that is to say, containing up to 5 grs. (0.35 Gm.) of active substance. If the pill is of larger size, it is called a *bolus*. Very small coated pills are spoken of as *granules*. Fourteen Pills and two Masses are official.

A pill consists of the active ingredient and of the *excipient* (cohesive); the latter varies with the nature of the former.

In order to make pills, the substance is first made into a *mass* by means of this excipient. The mass must be sufficiently soft to admit of molding, but on the other hand it should be sufficiently consistent not to lose its shape. It should neither harden nor soften nor crumble on keeping.

Method of Preparation.— The ingredients are first triturated to a fine powder. In case crystalline salts are used, these must first be desiccated. The excipient is then added in small portions and thoroughly triturated with the powder until the proper consistency is obtained. If accidentally too much excipient is added this can be remedied by the addition of some inert powder, such as starch, gum acacia, or powdered licorice. A great many substances may be used for excipients. The following are the most useful:

Liquid Excipients.— Glycerid of acacia or tragacanth, thick flour paste, glycerin, syrup, confections, or extracts.

Solid Excipients.— Acacia, tragacanth, starch, althæa, licorice powder, soap.

For chemicals which are destroyed by organic substances the best excipient is formed by a mixture of petrolatum and kaolin.

The weight of the finished pill should not exceed 0.5 Gm. (8 grains).

The mass having been formed by thorough trituration, it is placed on a glass or porcelain slab marked with equal divisions. It is well to put a little dusting-powder on the slab to prevent the mass from sticking to it. The best dusting-powders are starch, lycopodium, or licorice, according to the color of the pill mass. This mass is then rolled out by means of a broad spatula into a cylinder of uniform diameter, and this is cut with a sharp knife into the requisite number of equal parts. These are formed into spherical shape by rolling them between the thumb and the first two fingers. The finish may be rendered more perfect by placing the pills with a liberal amount of dusting-powder in the lid of the pill box and gently rolling them with the ball of the thumb. To disguise the taste of the pills one may make use of various coatings. The most popular of these are the sugar and the gelatin coatings. These can only be well done on a large scale. For the former, the pills are moistened with a thick syrup and rapidly rotated and dried in a current of warm air until they acquire a sufficiently thick coating and a fine polish. The latter is often enhanced by a little wax. For a gelatin coating they are dipped into a strong hot solution of gelatin, which is allowed to harden in the air. When it is desired to exclude the air from the pills, they are sometimes varnished by dipping them into an ethereal solution of tolu. This is the official process for keeping phosphorus pills. A still finer polish may be given to pills by coating them with silver leaf, which is done by shaking them in a box with silver foil. All of these coatings interfere with the absorption of the active substances, but this is indeed a disadvantage which adheres even to the uncoated pill. In some cases it is highly desirable that the pill reach the intestinal canal without any change — namely, when we desire a local action upon the intestinal canal alone. The following coatings may be employed for this purpose: (1) Keratin, which is made by dissolving goose-quill in acetic acid or sodium hydrate. (2) Salol. Both of these are partly dissolved in the stomach. (3) Glutoid capsules have also been recommended. They are gelatin capsules which have been hardened in formaldehyd.

The **pilulæ** of the B. P. are pill-masses (*massa,* U. S. P.).

Capsules are small containers, usually of gelatin, intended to be swallowed with the substance. Those used for powders are hard, and consist of a body and a cap. In filling these capsules, the powder is divided into the requisite number of parts, forced into the body with a spatula, and the caps placed on. Soft capsules are used for oils, etc. These are sealed with a drop of melted gelatin. These soft capsules may be made to hold as much as 4 Gms. Hard capsules should not hold more than 0.3 Gm. or at most 0.5 Gm. A somewhat larger amount may be used by making the powder into a pill mass. The purpose of capsules is to disguise the taste of the substance.

Wafers are thin sheets formed of a dried flour-paste, in which the powder is enveloped and swallowed. They possess the advantage that larger quantities of the drug (up to 1 Gm.) may be administered. When the wafers are molded into a form, they are called *conseals* or *cachets.*

Troches (*trochisci, lozenges*) are made by punching or cutting out circular or oblong disks from a mass made up from the active substance, sugar, and mucilage. These are then dried in the air. They are usually intended for solution in the mouth, and are most popular for throat medication. They are, however, sometimes used instead of pills. Nine troches are official.

Tablet triturates are small troches made from a mass of sugar of milk and dilute alcohol. This mass is spread into holes in a special form and then removed from these by means of a die. They have the advantage over pills of a very much greater solubility, and are the most convenient form of administering small doses of solid drugs, such as alkaloids, nitroglycerin, calomel, etc., by mouth. They are quite unsuitable for the administration of large doses. Manufacturers also prepare tinctures, etc., in tablet form, by evaporating the menstruum. This may interfere with the therapeutic efficiency. The various mixtures in tablet form, found on the price lists of pharmaceutic houses, will not be used as a rule by scientific physicians.

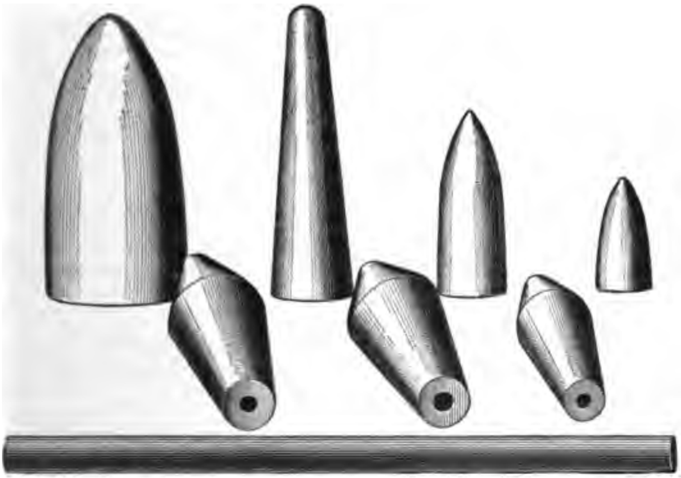

Fig. 42.— Different forms of suppositories (H. Blair). Natural size: The largest is for use in the vagina; the cylinder is a urethral suppository or bougie; the others are various shapes and sizes of rectal suppositories.

Hypodermic tablets are similar to the tablet triturates, especial care being exercised to secure quick solution.

Compressed tablets are made by compressing the substance diluted with sugar or sugar of milk. The material must be in granulated form. They do not break as readily as the triturates, but, on the other hand, they are not as soluble.

Lamellæ (B. P.) are thin gelatin disks, softened with glycerin, and impregnated with substances acting on the pupil. They are intended to be placed under the eyelids.

20. Suppositories are suitably shaped masses of solid, medicated, fatty substances, intended for introduction into the rectum, vagina, or urethra. They take the place of ointments for local treatment where these cannot be readily applied.

Suppositories are made by incorporating the medicinal substance into a suitable base, and molding into masses of suitable shape and size. The ideal base is one which, whilst solid at the ordinary temperature, is melted by the heat of the body. Such is cacao-butter (Oleum Theobromatis). Glycerinated gelatin or a soapy base is also sometimes used, especially with urethral suppositories, for which cacao-butter would be too brittle. Theobroma suppositories are made either by the hot or cold process. The hot process consists in melting cacao-butter at a temperature not exceeding 35° F. and adding the active substances, then pouring the mixture into cold molds. If the molds are sufficiently cold, the finished suppositories can be removed without any difficulty. It is usually advisable, however, to employ a small amount of dusting-powder. In the cold process the active substances are triturated with grated cacao-butter with the addition of a small amount of castor-oil, sufficient to make it into a suitable mass, which is then rolled out and divided as for pills. They may also be formed by pressure. *Suppository capsules,* whether of gelatin or of cacao-butter, largely defeat the object for which suppositories are employed. They are, however, much more convenient to prepare than the suppositories, and may suffice when the object is merely internal medication. Glycerin is made into a suppository by means of a very hard soap formed from stearic acid and sodium carbonate.

This is the only official suppository; but the U. S. P. supplies a general formula for others and specifies their weight: 2 Gm. for rectal; 4 Gm. for vaginal. Urethral suppositories are to be pencil-shaped, pointed at one end, and measure 7 or 14 Cm., weighing 2 or 4 Gm.

21. Ointments *(Unguenta)* are soft fatty masses intended for external application. They consist of the active ingredient and the base.

The base of ointments is formed by lard, by petrolatum, by lanolin, or by various mixtures, of which the "simple ointment," consisting of 4 parts of lard and 1 part of white wax, is the most important. The base must vary according to the object for which the ointment is employed, whether absorption, protection, or local action is desired. *Petrolatum* (vaselin), which consists of the less volatile parts of petroleum, is simply protective, or useful as a vehicle for substances intended to have a mere local action, since it is not absorbed. *Lanolin,* or its pharmacopœial substitute, Adeps Lanæ Hydrosus, consists of a mixture of cholesterin-like substances obtained from sheep's wool. It is very readily absorbed, does not become rancid, and mixes with its own weight of water. This latter property is of great advantage when it is desired to use crystalline salts in ointment form, since these can be incorporated in the form of solution, making a much smoother ointment. *Lard* is the cheapest ointment material. It possesses, but in a lesser degree, the advantages of lanolin. An important objection to it rests upon the fact that it becomes rancid very rapidly. This tendency can be greatly diminished by the incorporation of antiseptic substances. Official Benzoinated Lard is an attempt in this direction.

Ointments are prepared by fusion, mechanical admixture, and chemic reaction. In mixing ointments by fusion, that constituent of the ointment which has the highest melting-point is first melted, and the others are then added in the order of their melting-points. The active substance is added last, to obviate the prolonged action of heat upon it. The mechanical admixture is usually done on a slab or in a mortar. It is needless to say that powders must be in the finest stage of subdivision. If the quantity of powder is large, it is usually first mixed with some of the melted ointment.

Twenty-four ointments are official. The majority of medicated ointments contain 10%, some 20%, of the active ingredient. Ung. Chrysarobini, Iodi, Phenolis, and Veratrini are weaker; Hydrargyri, Picis Liquidæ, and Zinci Stearatis are stronger.

Cerates (U. S. P.) are preparations similar to ointments but of a firmer consistency. They are generally made from a mixture of wax and petrolatum, in the same manner as ointments. Six cerates are official.

22. Plasters are made by spreading on a thin cloth or leather support a mass or base which is hard at an ordinary temperature, but is softened and rendered adhesive at the temperature of the body. The base is fused and the active ingredients incorporated into it by stirring. Too great a degree of heat must, of course, be avoided. The mass is then usually spread upon pieces of linen, muslin, or leather. Plasters serve to afford protection to the skin, to bring together the edges of wounds, or to bring a drug in an absorbable medium into prolonged contact with the skin. Furthermore, the resins, etc., which frequently form the constituents of the plaster act as mild counterirritants. To avoid the rather excessive irritation resulting from the confinement of the secretions of the skin, plasters are now frequently made porous. A composition of rubber is the most common base of modern plasters. The typical old plaster, however, has for its base diachylon, Burgundy pitch, or other resins. Diachylon is a lead soap made by precipitating soap with lead acetate. This alone, or with the addition of a little rubber and petrolatum (Emplastrum Adhesivum) forms the base of the other six official plasters.

Plasters are now usually obtained from manufacturers, and are but rarely made to order.

To spread the plaster, the cloth, cut to the proper size and shape, is tacked on a board and the mass is heated and spread evenly with a trowel or spatula. A margin half an inch wide must be left to allow of handling. Isinglass plaster is made by spreading a thick solution of isinglass on silk.

Chartæ are medicated papers, *i. e.*, pieces of paper covered or impregnated with a medicinal substance. Charta Sinapis is used as a plaster, Charta Potassii Nitratis for fumigation.

23. Cataplasmata *(Poultices)*.— These are used mainly for the purpose of supplying heat. It is often necessary to give a patient directions for preparing them. Linseed poultices may be taken as a type: Pour a cup of linseed meal into 2½ cups of boiling water, stirring constantly. Spread the mush thickly on a piece of flannel, fold so as to form a sack, and apply as hot as can be conveniently borne. Cataplasma Kaolini is official.

The memorizing of the strength and doses of pharmaceutic preparations will be facilitated by the following tables:

TABLE IV.—STRENGTH OF PHARMACEUTIC PREPARATIONS.

U. S. P. *Opium:* Tincture, deodorized tincture, acetum, and Dover's powder = 10%; camphorated tincture = 2 grains to the ounce (= 0.4%).
Dilute Alcohol, 48.9% by volume.
Decoctions and Infusions, 5%.
U. S. P. *Dilute Acids,* 10% (except hydrocyanic = 2%; and acetic = 6%).
U. S. P. *Tinctures,* 0.4% to 50%; mostly 10% or 20%; all potent, 10%.
U. S. P. *Aceta,* 10%.
Fluidextracts, 100%.
Arsenic Solutions, 1%.
Solid Extracts, generally 400%.

TABLE V.—GENERAL DOSES OF PHARMACEUTICAL PREPARATIONS.

(ARRANGED IN ASCENDING ORDER.)

Poisonous Solid Extracts[1]	0.005 to 0.025 Gm.	(gr. $\frac{1}{10}$ to $\frac{1}{3}$)
Poisonous Fluidextracts;[1] *Liquores; Aromatic Oils; B. P. Hypodermic Injections*	0.1 to 0.7 c. c.	(♏ij to x)
Exceptions: Liquors of Alkaline Citrates and Acetates	30 c. c.	**℥j**
Non-poisonous Solid Extracts; Pill Masses	0.2 to 0.7 Gm.	(gr. iij to x)
Poisonous Tinctures and Wines;[1] *Liquid Opium Preparations; Dilute Acids*	0.3 to 1.3 c. c.	(♏v to xx)
Exceptions:[1] Tr. Aconite, Strophanthus, Cantharidis, Iodin.	0.2 to 0.5 c. c.	(♏iij to viij)
Tr. Opii Camphorata	to 15 c. c.	(℥ss.)
Ac. Hydrocyanic. Dil.	0.1 to 0.2 c. c.	(♏ij to iij)
Non-poisonous Fluidextracts; Spirits	2 to 5 c. c.	(ʒss to j)
Non-poisonous Tinctures, Wines, and Syrups	2 to 10 c. c.	(ʒss to ij)
Flavored Waters	5 to 15 c. c.	(ʒj to iij)
Infusions and Decoctions	15 to 120 c. c.	(℥ss to iv)
Exception: Infus. Digitalis	5 to 15 c. c.	(ʒj to iij)

(B) PHARMACEUTIC ASSAYING.[2]

Different samples of vegetable drugs may vary widely in the quantity of active constituents which they contain. These variations are most undesirable from a therapeutic standpoint, especially when they occur in potent, so called "*heroic*" drugs. Inorganic drugs or other definite chemic compounds are not subject to this variation; but in many cases the removal of the last traces of innocuous impurities would greatly increase their cost without adding to their therapeutic usefulness. The pharmacopœia has therefor aimed to furnish quantitative methods of estimation, assays, wherever possible, and to establish practical standards to which medicinal substances must conform. With inorganic drugs, it states the largest permissible quantity of innocuous impurities (usually less than 2%). With crude vegetable drugs, it states the lowest permissible percentage of active ingredient. Assayed galenic preparations are directed to be diluted so as to contain a definite proportion of active constituents, corresponding to the minimum permitted in the crude drug. These preparations should therefor be preferred to the crude drug whenever accurate dosage is desired.

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[1] In prescribing poisonous preparations, the exact dose must always be consulted (see Index).

[2] Exercise 9.

The *assay of inorganic drugs* involves the wellknown methods of ordinary quantitative analysis, volumetric processes being preferred. Special tests are furnished for determining the permissible limits of accidental *impurities,* and the presence of harmful substances, such as metals.

A series of volatile oils are assayed for their most important ingredient. Fats and fixed oils are tested for their "iodine absorption" and "saponification values"; resins for the "acid number"; some vegetable products for their ash. These tests serve mainly for identification and the exclusion of willful adulterations.

Pepsin is assayed for its digestive power for proteids, pancreatin for starch. In resinous drugs, such as Jalap, Scammony, or Guaiac, the proportion of ether- or alcohol-soluble matter is determined.

The most important class of assays refers to **drugs containing alkaloidal principles,** utilizing the method of immiscible solvents, as in toxicologic analysis. This rests on the fact that free alkaloids are generally soluble in chloroform or ether, whilst their salts are insoluble in these, but soluble in water. In principle, alkaloids are extracted by chloroform or ether, or a mixture of both, in alkaline reaction. This solution is then shaken in a separator with acidulated water, which converts the alkaloids into salts and dissolves them, leaving the impurities behind. For further purification, the watery solution is again rendered alkaline and extracted with chloroform or ether. This, on evaporation, leaves the fairly pure alkaloid which may be weighed; or titrated, by dissolving it in a known amount of acid, and titrating back with alkali. Each c. c. of acid corresponds to a definite quantity of each alkaloid (a table of these is given in the U. S. P., page 567).

The assay of Belladonna is typical of the details of the method.[1] It is important to observe the directions minutely to obtain reliable results. The process for extracts and fluidextracts differs merely in details (the percolation being omitted, etc.). Tinctures are first concentrated by evaporation.

This method estimates the sum of all the alkaloids present in the drug, and suffices when the important one predominates very largely over the others. When this is not the case, it is necessary to confine the assay to the particular alkaloid desired, generally a very difficult matter. In Hydrastis, advantage is taken of the comparatively greater solubility of hydrastin in ether; in Opium, of the comparative insolubility of the alkaloid in this solvent. In Nux Vomica, the brucin is removed by oxidizing it with nitric acid.

The following alkaloidal drugs and their preparations are directed to be assayed: Aconite, Belladonna, Cinchona, Coca, Colchicum, Conium, Guarana, Hydrastis, Hyoscyamus, Ipecac, Nux Vomica, Opium, Physostigma, Pilocarpus, Scopola, Strammonium. *In most of these, the*

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[1] See Exercise 9.

alkaloidal strength amounts to 0.35% *to* 0.55%. It is less in Physostigma, greater in Cinchona, Guarana, Hydrastis, Ipecac, Nux Vomica, Opium.

The following alkaloidal drugs are not assayed: Gelsemium, Granatum, Lobelia, Sanguinaria, Staphisagria, Veratrum.

Drugs which depend for their activity on neutral principles are unfortunately unsuitable for chemic assay; there being no reliable chemic method for estimating the constituents of Apocynum, Cannabis Indica, Convallaria, Digitalis, Ergot, Podophyllum, Rhamnus Purshiana, Rheum, Scilla, etc. Attempts have been made to supply this deficiency by **physiologic standardization,**— estimating the strength of a preparation by comparing its effects on animals with those of a standard product. A just fatal dose is generally the best criterion for quantitative work. These life-tests, however, are never as accurate as the chemic assay of alkaloids, on account of individual differences of susceptibility and absorption in different animals. These can be largely eliminated by using an extensive series of animals; but the expense and labor is scarcely warranted by the results, except in a very few cases, for instance with Digitalis. Qualitative physiologic tests of drugs of very uncertain activity, such as Cannabis Indica or Ergot, are more simple and deserve to be encouraged. The only physiologic test thus far recognized by the pharmacopœia refers to the standardization of antidiphtheric serum.

(C) TABLES OF INCOMPATIBILITIES AND SOLUBILITIES.

I. INCOMPATIBILITY.[1]

This is a subject usually very confusing to the student, since it consists of what appears at first sight a vast array of details. However, it rests only upon an application of the ordinary chemic reactions, and when the latter have been mastered, the subject is comparatively easy and simple. It may be laid down as a general rule that substances are incompatible if they are used in testing for each other or if they form antidotes.

In the following compilation it has been attempted to arrange the incompatibilities into general groups.

In this generalization, it is not feasible to take account of individual exceptions. Care has been taken to err on the safe side. It is much more important for the physician to remember that mercuric chlorid is generally incompatible with alkaloids, than it is to know that it may be prescribed with some.

Incompatibility is said to exist *when the constituents of a mixture interfere with one another in a way not intended by the prescriber.*

If such an interference is intentional, it is called an *intentional incompatibility,* as in the preparation of "yellow wash."

If a chemical change occurs, the incompatibility is called *chemical.*

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[1] Exercise 8.

When it consists in a precipitation of the substance by a change in the solvent, or when a chemic incompatibility does not interfere with the active substance, but produces an unsightly appearance, it is *pharmaceutic.*

If the interference is with the solubility, or if liquefaction or deliquescence occurs, the incompatibility is *mechanic.*

When without causing any chemic changes it interferes with the physiologic action of the ingredients, it is *therapeutic.*

TABLE VI.—THE MOST IMPORTANT INCOMPATIBILITIES, ARRANGED BY GROUPS.

(A) Chemic Incompatibility.— (I) Explosive; (II) Precipitation; (III) Production of body with undesired properties.

I. Explosives.—

1. Spontaneously inflammable substances (phosphorus).
2. Substances which explode on heating ($KClO_3$, acetozone, benzozone).
3. Substances which explode on mixing (3). (See below.)
4. Substances which cause a more gradual evolution of gas (4).
5. Substances which cause an evolution of heat (H_2SO_4 and water).
6. Substances which should be guarded from fire (ether, alcohol, benzin, collodion, turpentine, camphor, essential oils, etc.).

3. SUBSTANCES WHICH EXPLODE ON MIXING:[1]

(*a*) *Substances containing loosely combined oxygen,* such as: *Chromic acid; Concentrated nitric acid and nitrates; Permanganates; Chlorates, bromates, or iodates; acetozone, benzozone:*
with easily oxidizable substances, such as: All organic substances; Sulphur, sulphids, sulphites, and hyposulphites; Iodin and iodids; Phosphorus, phosphites, and hypophosphites; Reduced iron.

(*b*) *Iodin* (with any oxidizing agent); also with Ammonia or turpentine.

(*c*) *Chlorin:* with NH_4Cl.

EXPLOSIVE MIXTURES.

Explosions will only occur when the substances are dry, or at least concentrated, and when they are heated or percussed.

Dilute solutions may be mixed without danger if not heated. Glycerin, phenol, and in some cases alcohol, behave like dry solids.

Permanganate of potash or chromic acid or nitrate of silver will decompose organic substances even in solution, but in this case without explosion. Acetozone will cause explosion.

Powders may be mixed without concussion, but even this should be avoided, since conditions favorable to explosion may arise after they leave the hands of the dispenser.

Pills containing these easily decomposed substances are best made with inorganic excipient (clay and vaselin).

Substances containing loosely combined oxygen may explode on concussion or heating when no reducing substances have been added; this is due to their containing dust or other organic matter. They should therefore be handled with care.

4. SUBSTANCES WHICH CAUSE A GRADUAL EVOLUTION OF GAS:

HCl with HNO_3.
Strong acids with $KClO_3$ (Cl).
Strong acids with alcohol (esters).
Acids with carbonates (CO_2).
Acids with sulphids (H_2S).

II. Incompatibility by Precipitation.—

1. The following INORGANIC BASES or their salts precipitate the following INORGANIC ACIDS or their salts:

(*a*) *Salts of metals and earths* are precipitated by HO, O, CO_3, P_2O_5, BO_3, oxalic acid, and the corresponding salts of alkalies.
(*b*) *Salts of metals:* by the above salts of earth; also by sulphids, arsenates, arsenites, and tannin.
(*c*) *Mercury salts* should not be prescribed in solution with other metals, as a general rule.
(*d*) *Salts of Ag, Hg(ous), Pb:* by Cl, Br, I. (*$HgCl_2$* also precipitates by iodids, soluble in excess of reagents).
(*e*) *Salts of Pb, Ca, Sr, Ba:* by SO_4. Strong solutions of Ag. are also precipitated by SO_4.

2. The following SALTS OF METALS precipitate the following ORGANIC SUBSTANCES:

(*a*) *All metallic salts:* proteids, tannin, acacia.
(*b*) *Some metallic salts* (especially double salts): alkaloids.
(*c*) *Silver salts:* all organic substances.
(*d*) *Iron salts:* salicylic or carbolic acid or their salts produce a purple color.

3. ORGANIC SUBSTANCES: The following incompatibilities by precipitation are important:

(*a*) *All* are incompatible with oxidizing agents (compare explosives) and with silver salts.
(*b*) *Alkaloids, proteids, and tannin* are precipitated by
  Many metallic salts, especially mercuric.
  Double iodids or bromids and free iodin.
  Picric and salicylic acid, and borates.
Alkaloidal salts, in addition, by free bases and carbonates.
Strychnin salts, by bromids and iodids.
Alkaloids and proteids, by tannin.
Acacia, gelatin, and proteids, by alcohol, borax, Tr. ferri chloridi.
(*c*) *Antipyrin:* by same precipitants as alkaloids.
  By KI.
  Fe_2Cl_6 = reddish color.
  Spirits of nitrous ether = green color or precipitate.
(*d*) *Chloral:* when in alcoholic solution by strong solutions of salts, especially bromids.
  Alkalies cause decomposition.
  Camphor, in dry state = liquefaction.
Camphor and the coal-tar antipyretics also liquify with menthol, thymol, salol, and naphthol.
(*e*) *Salicylic acid,* by iron salts, iodids, and some alkaloids.
Salicylates, benzoates, and borates are precipitated by free acids.

(f) *Tannin,* by metallic salts,[1] alkaloids, gelatin and albumin, carbonates.

III. Production of a Substance with Undesired Properties.—

(*a*) Iodids, Bromids, Iodates, Bromates, Chlorates: with strong mineral acids or strong oxidizing agents, such as $KClO_3$, H_2O_2, HNO_3, $KMnO_4$ = production of I, Br, or Cl.
(*b*) Glucosids with acids.
(*c*) Chloral with alkalies (= chloroform).

(B) Pharmaceutic Incompatibilities.—

1. *Alcohol* should not be added to:
   Acacia, gelatin, proteids, emulsions, strong salt solutions.
2. *Water* should not be added to:
   Alcoholic liquids in general (such as tinctures, spirits, fluidextracts).
   Ethereal liquids (oleoresins), oils.
   (Carbolic acid should not be mixed with collodion.)
3. *Glycyrrhiza* and acids.

The following drugs are almost universally incompatible, and should therefore be prescribed alone, if possible:

Strong mineral acids,
$HgCl_2$,
KI,
$AgNO_3$,
$Pb(C_2H_3O_2)_2$,
$KMnO_4$,
Alkaloids,
Tannin.

(C) Therapeutic Incompatibility.—

For example: Pilocarpin and atropin.

II. SOLUBILITIES.

It is well to have a general idea of the solubility of the substances usually prescribed. The subjoined compilations will be found useful in this connection. A knowledge of analytic chemistry and of incompatibilities can also be utilized here, for a substance appearing as a precipitate is, of course, relatively insoluble.

TABLE VII.—GENERAL SOLUBILITY OF SALTS IN WATER.

Only those commonly prescribed are included (not those which are formed only in incompatible prescriptions).

I. Arranged by Acids.—

Group A: Salts Mostly Soluble.—

1. *Acetates and Nitrates:* all soluble (except bismuth subnitrate).
2. *Halogen group* (= iodids, bromids, and chlorids): Soluble, except Ag; Hg (ous); Pb; Bi.

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[1] The incompatibility of *tannin with iron* is especially important, since it is often desirable to administer iron salts with a bitter substance. Practically the only tannin-free bitters are *Calumba, Quassia,* and *alkaloids.*

De-tannated preparations, such as the *Elixir of Gentian* N. F., may also be employed.

3. *Sulphates:* Soluble, except Pb, Sr, Ba; Ca sparingly soluble.
4. *Tartrates and Citrates:* mostly soluble.

Group B: Salts Mostly Insoluble.—

1. *Arsenates*
Arsenites
Carbonates
Hydrates (Ca sparingly soluble)
Oxids
Oxalates
Borates
Phosphates
} Insoluble, except those of alkali metals.

II. Arranged by Base.—

The salts considered in this table are: Acetates (Ac), Halogens (H), Oxids (O), Sulphates (SO_4), Phosphates (PO_4), Oxalates (Ox), Carbonates (CO_3), Sulphids (S), Nitrates (NO_3), Citrates (Ci). Hydrates agree with oxids.

Those of the above salts which are *not mentioned* with the respective base are *insoluble*.

1. *Alkali Metals* (= Na, K, NH_4): all soluble. .
2. *Lithium:* Soluble, except O and CO_3, sparingly soluble, and PO_4, insoluble.
3. *Mg, Al:* Soluble: NO_3, Ac, H, Ci, SO_4, S.
4. *Ca, Ba, Sr:* Soluble: NO_3, Ac, H, Ci, S; sparingly: O.
5. *Zn, Mn, Ni, Co, Fe Hg (ic), Cu, Sn* } Soluble: NO_3, Ac, H, Ci, SO_4 (mercuric iodid is insoluble).
6. *Ag:* NO_3, SO_4.
7. *Pb:* NO_3, Ac.
8. *Bi, Sb:* Only soluble in form of double organic salts (*e. g.*, Bismuth and Ammonium Citrate; Antimony and Potassium Tartrate.
9. Mercurous: Insoluble.

III. Strength of Watery Solution, in which commonly used salts may safely be prescribed.—(It must be remembered that where several salts are prescribed in the same mixture, the solubility of each is apt to be lowered.)

The exact solubility of important substances will be found in the appendix.

The following table gives the amount of very commonly used drugs which can be *safely prescribed in water enough to make 100 c. c.* These should be memorized:

50 Gms: (=ʒiv in water q. s. ℥j) Tannin; Antipyrin; Acetate, Citrate, Salicylate, Iodide or Bromide of Potassium or Sodium; $AgNO_3$; $ZnSO_4$; Chloral; Cocain Hydrochlorid.

5 Gms: (=25 grains in water q. s. ℥j) Alum; Carbolic Acid; Borax; $KClO_3$; $NaHCO_3$; $HgCl_2$; Tartar Emetic; Quinin Bisulphate; Citrated Caffein; the majority of the soluble salts of alkalies, earths, and metals.

Smaller Quantities: Boric Acid, 4; Morphin Sulphate, 4.5; Quinin Hydrochlorid, 3; Quinin Sulphate, 0.13; Strychnin Sulphate, 2.

IV. Solubility in Different Media.—

As a general rule, *inorganic substances* are more soluble in water than in alcohol.

Basic alkaloids are insoluble in water, more soluble in alcohol.

Alkaloidal salts are soluble in either alcohol or water.

Gums are soluble in water, insoluble in alcohol. *Resins* and *essential oils* are the reverse.

(In making mixtures, it must be remembered that spirits, tinctures, and fluidextracts all contain alcohol.)

Glycerin stands intermediate between alcohol and water as a solvent.

The following substances are:

1. Practically insoluble in water: Iodin, calomel.

2. Soluble in water, but almost insoluble in alcohol: Alum, NH_4Cl, $KClO_3$, tartar emetic, $ZnSO_4$, Borax.

3. Much more soluble in glycerin than in water: Boric acid, alum, carbolic acid, $HgCl_2$.

CHAPTER V.

TOXICOLOGY.

Toxicology is that part of pharmacology which treats of poisons.

The details of the actions of poisons will be considered in part II, in connection with the individual poisons, but a general outline of toxicological analysis and of the treatment of poisoning may find a place here.

Definition.— A poison (from potion, a draught), by the broadest definition, is a substance the administration of which is injurious to health. However, injurious mechanical, physical, or bacterial agencies are not commonly classed as poisons; nor are the substances which produce injurious effects only in very large doses (say over 50 Gms.). It is very difficult to give a definition which will not be ambiguous in some cases. The following covers most of the points which must be considered in classing a substance as a poison:

A poison is any substance which, acting directly through its inherent chemic properties, and by its ordinary action, is capable of destroying life, or of seriously endangering health, when it is applied to the body, externally, or in moderate doses (to 50 Gms.) internally.

Etiology of Poisoning.— Poisoning may result through criminal or suicidal intent, or through accident. The statistics of the relative frequency of the different forms of poisoning vary from year to year, and with each country. Suicidal poisoning is probably the most frequent, nearly a half of the suicides in the United States being due to poisoning.

It is calculated that here five-sixths of all suicidal cases are due to carbolic acid. There is, however, a fashion in poisons, as in other things. This is greatly fostered by the notoriety which the newspapers give to these cases.

Symptoms of Poisoning and Classification of Poisons.— *Suspicion of poisoning* is aroused if a person, previously in good health, manifests rather suddenly marked pathologic symptoms, which become rapidly worse. The suspicion becomes more firm, if the phenomena appear a short time after swallowing some substance which may perhaps have an unusual odor or taste;[1] if they agree in character with those produced by some group of poisons, and if they do not agree with any other disease.

With reference to these symptoms several **classes of poisons** are quite well defined:

1. **Irritants.**— These produce inflammation; if they are taken by the mouth, there is pain throughout the alimentary canal, vomiting, purging, delirium, coma. Most poisons are to some extent irritant, so that these symptoms are almost universally present. The irritants can be subdivided into *corrosives,* which produce a direct destruction of tissues; and *simple irritants,* which do not. If corrosives are taken by the stomach, the vomit is often bloody.

2. **Nerve Poisons.**— These act on the neuromuscular apparatus, and include most of the poisons which are fatal in minute doses. They are subdivided into: **Convulsants,** which cause spasms; **Somnifacients,** causing sleep and coma; and **Cardiac poisons,** which stop the heart.

3. **Blood Poisons.**— Those which alter the hemoglobin or blood corpuscles. These include the toxic gases, the nitrites, etc. Their action is generally characterized by cyanosis.

It must not be supposed that the action of a poison is confined generally to one class of structures or functions. All functions suffer directly or indirectly, and whatever the class to which the poison belongs, the final **cause of death** is, in almost all cases, a paralysis of respiration, preceded by the phenomena of *asphyxia.* In virtue of the latter, or through other causes, the urine often contains sugar.

The irritants, and especially the corrosives, produce lesions which can be demonstrated at AUTOPSY. With other poisons the post mortem examination is generally negative. The SPECTRUM OF THE BLOOD shows characteristic changes with some poisons. These are also apt to cause ecchymotic discolorations of the skin. Antiseptic poisons *delay the putrefaction* of the body, so that mummification may result. Convulsive poisons quicken the onset of *rigor mortis.*

Duties of the Physician in Cases of Poisoning.— These are twofold: to save life or suffering, and to forward justice. The former object requires the removal of the poison, the administration of chemical antidotes, and the treatment of the symptoms.

For the *detection of the poison,* and to aid in fixing the guilt on the proper person, the physician must carefully observe the symptoms, take possession of any suspected material, medicine, vomit, etc., and in case of autopsy, preserve the stomach and its contents, the intestines and contents, blood, liver, kidneys, and portions of other organs, *separately,* without antiseptics,[2] in clean, hermetically closed, glass vessels, which should be sealed with wax.[1] An exact *written record* of all the observations should be made as soon as possible.

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[1] It may appear strange that poisons which possess a pronounced and disagreeable taste could be used for criminal poisoning, except with infants; but a moment's thought will show that if a liquid is taken unsuspectingly, the taste is not noticed until a large amount has been swallowed.

[2] Even glucosid and alkaloid poisons can be isolated for a long time (160 to 270 days) from putrifying masses. Some poisons, however, disappear rapidly (Phosphorus, Cyanid, Picrotoxin, Phenol, &c). Strychnin and morphin are very persistent.

The *symptoms* in cases of suspected poisoning are very rarely sufficient to affirm the presence or nature of a poison, although they may be of great aid to the analyst. The final proof rests generally as the results of the *chemic examination*. So much depends on this analysis, that it should never be undertaken by anyone who has not had extensive experience in this class of work, and who has not the necessary facilities. It lies entirely outside of the scope of the practicing physician. The latter should, however, be familiar with the general outline of the process used for isolating poisons; and with such chemic tests as may be quickly applied. These tests are often valuable for diagnostic and therapeutic purposes. The physician is also expected to give expert testimony on toxicologic questions, and to do this intelligently, he must have at least an elementary knowledge of toxicologic analysis, such as is furnished in the following section.

Some poisons can be demonstrated much better by tests on animals than by any chemic tests. For this object, they should be isolated in as pure a form as possible, by the methods laid down in this section. The application of these life tests, which have not hitherto received the attention that they deserve, falls peculiarly into the province of the scientifically trained physician.

OUTLINE OF TOXICOLOGIC ANALYSIS.[2]

The first duty of the analyst is to guard the material confided to him from *the wilful or accidental introduction of poisons*. For this purpose, precaution must be taken that no other person has access to the material; and every reagent and apparatus must be tested personally.

As a rule, the different organs must be kept strictly separated throughout the analysis. It will depend on circumstances whether the analysis of the individual organs is made at the same time, or successively. If the latter is decided on, the largest organ, or that most likely to contain the poison, is examined first. It may be advisable, however, to mix a weighed quantity (one fourth or one third) of the communited organs, and to use this mixture for the first analysis.

Since the material to be analyzed is usually limited in amount, and cannot be replaced, the examination must be arranged in such a way that as many tests as possible can be made successively on a single sample of the material. An economy of time and material is also secured by obtaining, as quickly as possible, some idea of what poisons may be present. This may be done by some easy preliminary tests, or by using so-called "group-reactions" which, if negative, will exclude a number of substances. The symptoms may also have furnished some important hints, but should never prevent the complete examination of the substance.

During the isolation and the preliminary search for the poison, only the most important tests should be applied. When the poison has been isolated, however, it should be subjected to every known test. A sample of the isolated poison should be preserved, in stable form.

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[1] In emergency, a rare or specially marked coin, or a key, may serve to impress the seal.

[2] This section should be studied in connection with the practical exercises 9 to 14.

The **Systematic Examination** is begun by a careful inspection of the portions of the alimentary canal. These are opened, and extended on an inverted evaporating dish, mucous surface upward. Pathologic lesions are looked for, as also particles of the poison which may be adherent. A magnifying lens should be employed. (Granules of arsenic have often been isolated in this way.) The contents of the alimentary canal, or vomited matter, are subjected to a similar close inspection. The odor should be carefully observed.

During this examination, the **reaction to litmus paper** should be noted (caustic acids or alkalies).

Each organ is then hashed, carefully weighed, and replaced in hermetically sealed jars.[1]

For the actual isolation of the poisons, each **organ is divided into several parts,** carefully weighed. If the quantity of material is very scanty, two equal portions will suffice: one is reserved for preliminary tests, easily decomposable poisons, and control; the other is examined successively for easily volatile poisons, for fixed organic poisons, and for metals.

Ordinarily, four equal portions may be made: I. Volatile poisons; then for metals. II. Fixed organic. III. Preliminary tests and destructible poisons. IV. Control.

Volatile Poisons.— A portion of the material is acidulated with tartaric acid (adding water if necessary), and distilled from a flask or retort connected with a Liebig's condenser.[2] It is advisable to pass a slow current of live steam through the mass. The distillation is continued until about two-thirds of the liquid have been collected. The distillate is collected in three portions, and tested.

The principal preliminary tests which are to be applied to the distillate are: the odor (volatile oils, chloroform, ether, turpentine, etc.); phosphorus (see below); carbolic acid (Exercise X, No. 18*c*); HCN (Ex. X, No. 27*b*); alcohol (Ex. X, No. 29)[3]; chloroform and chloral (Ex. X, Nos. 30 and 31).

The odorous principles and hydrocyanic acid are generally found in the first fraction of the distillate, phenol and chloral in the last.

Phosphorus.— A preliminary test for this element must be made with the silver nitrate and lead acetate papers (see Exercise 10, No. 33), before the distillation is begun. If this test indicates its presence, the condenser is set upright (Fig. 43), and the distillation is carried on in a darkened room. All air is expelled from the apparatus by a stream of carbon dioxid. This is then shut off, and replaced by live steam, the flask being heated at the same time. If phosphorus is present, a luminous ring appears in the tubes or condenser, shifting its position when the heat applied to the flask is altered (*Mitscherlich's Method*). The appearance of this phenomenon proves the presence of phosphorus absolutely.

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[1] As soon as the absence of volatile poisons has been proven, the contents of the jars may be covered with 95% alcohol.

[2] See below for special arrangement to be used when phosphorus is present.

[3] Alcohol is only important if it is present in large amounts, such as would be indicated by the test 29c. Smaller quantities may be present accidentally or as antidote.

There are, however, quite a number of substances the presence of which interferes with the formation of this ring. Almost any volatile substance may do so; turpentine, chloroform, ether, alcohol; and alcohol is often present, as it is usually given as an antidote.

The absence of the ring does not, therefore, prove the absence of phosphorus. The distillate will contain phosphorus in the lower stages of oxidation, as phosphorus or hypophosphorous acid. The best way to prove phosphorus in this is to add some bromin water to the distillate and to evaporate to dryness. This results in phosphoric acid, which may be demonstrated by magnesia mixture or ammonium molybdate. The quantitative determination of phosphorus is not important; because if it is present at all, it is present as a toxic agent.

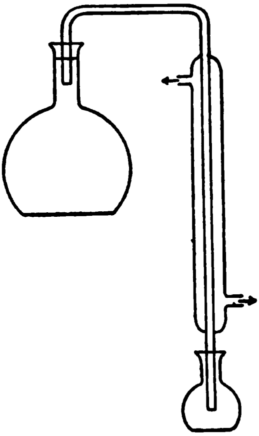

Fig. 43.— Mitscherlich apparatus.

Cyanids.— The presence of mere traces of hydrocyanic acid in the distillate is no proof of poisoning, since these may have been introduced in the way of food (almonds or other seeds). A *quantitative estimation*, by means of silver nitrate, may be necessary. The qualitative proof also requires two further precautions:

With the method which we have given, ferrocyanids might also be decomposed and give rise to hydrocyanic acid; and since ferrocyanids are not toxic, this would lead to wrong conclusions. To eliminate this, the original liquid is filtered and the Prussian blue test applied to it directly. Mercuric cyanid does not yield its hydrocyanic acid in this treatment. If it is suspected, the material must be treated with hydrogen sulphid.

Distillation from Alkaline Solution.— It is sometimes recommended to add water to the residue in the retort, to make it alkaline with sodium carbonate, and to distill again. The distillate contains ammonium, amines, chloroform (if chloral was present), and the volatile alkaloids. This step may generally be omitted, as these poisons are discovered in other parts of the process; or a small sample may be heated in a test-tube with sodium carbonate, and the odor noted.

Extraction of Fixed Organic Poisons.—The extraction, separation and purification of these poisons are based on their special solubility in certain solvents. As a rule, they are all fairly soluble in acidulated water and alcohol. The neutral principles are removed from the acid watery solution by ether or chloroform. The alkaloids are only dissolved by these substances after the addition of an alkali.

Various methods are in use. The most practical is that of **Stas-Otto,** slightly modified:

§ 1. The poisons are first *brought into solution* by boiling the material, if solid, with about five parts of water for fifteen minutes (or the residue remaining after the distillation of the acid solution may be used). The mixture is cooled and strained. This *removes fat, coagulable proteid, fibre, etc.*[1]

§ 2. The strained solution is evaporated at a low temperature to a syrupy consistency, and boiled with twice its volume of alcohol, for fifteen minutes. The evaporated alcohol is replaced. It is then filtered, and the filter washed with alcohol. This *removes salts, non-coagulable proteids, etc.*

§ 3. The alcoholic filtrate is diluted with an equal volume of water and filtered. This *removes resins, fats, etc.* (The residue may be examined for cathartic resins and croton oil.) (For further purification, the filtrate may be again treated by §§ 2 and 3.)

§ 4. The filtrate, which should have an acid reaction, is now shaken in a separatory funnel with 10 c. c. of ether. This is drawn off, and the same process is repeated twice. The ether *removes neutral principles, picric acid, and salicylic acid.* It is filtered and allowed to evaporate in a glass capsule, and the residue is purified and tested for these acids, for caffein, cantharidin, colchicin, digitalin, picrotoxin, and the coal-tar antipyretics.

§ 5. The watery solution, remaining from the extraction with ether in the last paragraph, is now made fairly alkaline with sodium carbonate (*to liberate the alkaloids*) and again extracted with ether, as in the last paragraph. From this alkaline solution, the ether *removes all alkaloids except morphin.* The ethereal layer is filtered and evaporated, the residue is purified, and tested, first by potassium mercuric iodid, then for physostigmin, apomorphin, nicotin, coniin, veratrin, strychnin, brucin, atropin, cocain, codein, narcotin, emetin, and aconitin.

§ 6. *To isolate the morphin,* the watery liquid remaining in the last paragraph, is made acid, then alkaline by ammonia, and shaken at once with acetic ether, or with *hot* amyl alcohol.

§ 7. To test for *oxalic acid,* the original substance is partly dried, extracted with 5 c. c. of dilute hydrochloric acid and 20 c. c. of boiling alcohol, for half an hour, filtered, evaporated, extracted with water, and tested by Ex. 10, No. 25. *Santonin* and *Meconic Acid* must also be extracted by special methods.

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[1] It goes without saying that the remaining mass should be washed, in every instance of filtration or straining.

Dragendorff's Method.— In this, a more extensive separation of the poisons is obtained, by multiplying the solvents and operations. The preliminary treatment is as per §§ 1, 2, and 3. The acid solution is then exhausted successively by the following solvents:[1]

SOLVENT:	The RESIDUE left by the evaporation of the solvent is:
Petroleum Ether	Volatile: Phenol and essential oils. Amorph.: Capsicin. Cryst.: Volat.: Picric Acid, Piperin. Cryst.: Colorless, Fusible, and Odorless: Camphor.
Benzol	Amorph.: Colorless or Pale Yellow: Colocynthin, Elaterin, Populin. Amorph.: Yellow: Chrysammic Acid, Colchicine, Quassiin. Cryst.: Colorless: Berberine, Cantharidin, Cascarillin, Cubebin, Digitalin, Santonin, Theine. Cryst.: Yellow: Aloetin (Picric Acid, Piperin).
Chloroform	Amorph.: Convallamarin, Digitalin, Jervine, Saponin, Senegin, Smilacin, Syringin. Cryst.: Cinchonine, Helleborin, Narceine, Papaverine, Picrotoxin, Theobromine.

The watery fluid is now rendered alkaline, and again extracted successively by these solvents:

SOLVENT:	RESIDUE:
Petroleum Ether	Aniline, Brucine, Coniine, Emetine, Lobeline, Methylconiine, Nicotine, Quinine, Sabadilline, Sarracenine, Sparteine, Strychnine, Trimethylamine, Veratrine.
Benzol	Aconellin, Aconitine, Atropine, Brucine, Cinchonine, Codeine, Delphinine, Emetine, Ethyl-strychnine, Hyoscyamine, Methyl-strychnine, Napelline, Narcotine, Nepaline, Physostigmine, Quinine, Sabadilline, Sabatrine, Strychnine, Thebaine, Veratrine.
Chloroform	Celandine, Cinchonine, Morphine, Narceine, Papaverine.
Amyl Alcohol.	Convallamarin, Morphine, Narceine, Salicin, Saponin, Senegin, Solanine.

Kippenberger's Method.— This possesses the advantage of separating the poisons in purer form from the start, but it involves technical difficulties. It depends on the insolubility of the tannates of proteids in glycerin, whilst the organic poisons are soluble in this medium. The solid material (say 100 Gm.) is digested for two days at 40° C. with 10 Gm. tannin, 1 Gm. tartaric acid, and 100 Gm. glycerin. The mass is expressed; the residue is washed with tannic glycerin. The fluids are diluted with water, heated to 50° C., and filtered. The filtrate is then extracted twice with petroleum ether, which removes mainly fats. The glycerin layer is then extracted as in the Stas-Otto method (§§ 4 and 5), but using chloroform in place of ether.

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[1] In this table the alkaloids are distinguished from the neutral principles by spelling the alkaloidal names with a final *e*.

For *the purification of the alkaloids,* the residue, left by the evaporation of the chloroform, is dissolved in acidulated water, neutralized, and at once precipitated by iodin-potassium-iodid. The precipitate is collected on a small filter, washed with cold water, dried, and dissolved in hot acetone. The filtered acetone solution is treated first with alkali, then with acid, then with water; the acetone is expelled on a water bath, and the remaining watery solution is decolorized by sodium hyposulphite. The solution is then made alkaline with sodium carbonate and extracted with ether or chloroform.

Physiologic Tests.— The poisons isolated by these methods are often not sufficiently pure to give the typical chemic tests; furthermore, certain of the tests are closely simulated by ptomains. This holds true also of the physiologic tests, i. e., the effects on animals.

These similarities have been found with the following: coniin, colchicin, atropin, delphinin, digitalin, morphin, nicotin, veratrin. The only way to distinguish with certainty between these is to use both the chemic and the physiologic tests. For, as far as is known, there are no ptomains which give both the chemic and physiologic tests of one alkaloid.

The physiologic tests can generally be obtained with fairly impure preparations. They are most typical in the case of strychnin, atropin, physostigmin, aconite, digitalis group, picrotoxin, veratrin, cantharidin, croton oil.

Isolation of Fixed Inorganic Poisons.—The absence of many metallic poisons can be quickly shown by Reinsch's test (see Exercise X, No. 32). This does not, however, dispense from further tests.

The residues of the preceding operations may be used for the search of these poisons. The usual methods of inorganic analysis are followed; but it is superfluous to test for non-poisonous constituents. Only an outline can be given here:

A: Destruction of Organic Matter and Solution.—*Method of Fresenius and Babo.*—Organs or syrupy residue, plus 300 c.c. to 500 c.c. of arsenic free HCl (1 : 2) in liter flask: heat lukewarm. Add 4 to 6 Gm. $KClO_3$ in 0.5 Gm. portions, till dissolved. Evaporate to about 100 c.c. (no free Cl). Dilute to 400 c.c. Add 2 c.c. dilute H_2SO_4. Stand overnight. Filter. *Filtrate* = *B. Residue* = *K.*

Filtrate B.— Pass through filter water to just 500 c.c. Use 50 c.c.

for Marsh's test (see *L*). If *As* is present, use balance for quantitative (see *C*). If not, evaporate small sample, dissolve in 10 c. c. water, add NH_4OH: blue = **Cu.**

C.—Heat balance of filtrate B to 80° C. and pass arsenic free H_2S[1] for 2 or 3 hours, until cool. Heat again, and repeat. Stopper and set aside in warm place for 24 hours. *Precipitate* may contain **As, Sb, Hg, Cu, Pb.** It may be used for the quantitative estimation of As, or for further identification by *D*. *Filtrate* = *I*.

D (*H_2S precipitate of C*).—Wash with H_2S water, warm with 4 c. c. ammon. sulphid, 4 c. c. ammonia, 8 c. c. water. Filter. *Filtrate* = *E*; *Insoluble* = *F*.

E (*Filtrate of D*).—Evaporate to dry; heat with HNO_3 till pure yellow; heat to expel HNO_3; add Na_2CO_3 and $NaNO_3$; fuse; extract with boiling water; add 2 Gm. $NaHCO_3$; filter; *Filtrate* contains **As** and may be used for quantitative. The *insoluble* = **Sb:** apply tests.

F (*Insoluble of D*).—Oxidize residue and filter in capsule with HCl and $KClO_3$; filter; dilute; heat; pass H_2S; filter; wash precipitate with warm HNO_3. *Filtrate* = *G*. *Precipitate* = *H*.

G (*Filtrate of F*).—Add 10 drops dilute H_2SO_4; evaporate; take up with water. *Residue* = **Pb:** *Filtrate* = **Cu.** (Apply tests.)

H (*Precipitate of F*).—Oxidize with aqua regia; evaporate; filter; dilute; test for **Hg.**

I (*Filtrate of C*).—Use half for zinc, half for chromium.

Zn: Neutralize with KOH; acidulate with $H_2C_2O_2$; precipitate with H_2S; wash precipitate with $H_2C_2O_2$ in H_2S water (1 : 5); incinerate, precipitate and filter; dissolve in dilute H_2SO_4, plus a little HNO_3; evaporate dry; dissolve in H_2O; test for **Zn.**

Cr: Evaporate to just moist; mix with KNO_3; dry; fuse; dissolve; test for **chromate.**

K (*Residue of A*).—Fuse with KNO_3, Na_2CO_3, and NH_4NO_3. Suspend in H_2O; pass CO_2; boil; filter. Dissolve precipitate in dilute HNO_3. Test this solution for **Ag, Ba,** ***and*** **Pb.**

L: Marsh's Test (*see B*).—Produce hydrogen in flask by acting on pure zinc with arsenic free HCl; pass through $CaCl_2$, through tubes drawn out at several places. Heat to redness at the thick portion of a segment. (This blank test should be continued for six hours.) If no mirror appears, introduce the suspected solution. Black mirror occurs with arsenic or antimony. They may be distinguished as follows:

ARSENIC:	ANTIMONY:
Mirror beyond heated portion.	Mirror *at* heated portion
Garlic odor on heating in air.	No odor.
Dissolves in hypochlorite.	Not.
Easily volatilized when heated in hydrogen.	Not easily volatilized.
Heated in air, yields easily volatilized white crystals.	Amorphous white residue, not easily volatilized.
Heated in H_2S, yellow, insoluble in HCl.	Red (black on strong heating); soluble in HCl.
Dissolved in HNO_3, evaporated, plus $AgNO_3$, plus vapor of NH_3, red or yellow precipitate.	No color in cold; black (metallic Ag) on heating.

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[1] H_2S purified by passing through water, calcium chlorid, and a tube, 30 cm. long, filled with alternate layers of glass-wool and iodin crystals.

TREATMENT OF POISONING.[1]

Whilst every case of poisoning demands to be treated by itself, yet certain general principles are all but universally applicable. These are the more important since the nature of the poison is so often unknown.

The first peculiarity of poisoning to deserve especial attention is the rapid course. This demands that whatever measures are taken, they *must be taken quickly*. The physician should therefore be thoroughly familiar with the general rules of treatment, so that no hesitation or delay occurs. On this account also, the antidote nearest to hand should be used in preference to one which can only be obtained with delay, even if the latter should be theoretically preferable.

The treatment of poisoning is directed against the cause and the symptoms. The former consists in *removing the poison*, or in *rendering it harmless*. Since neither of these objects can usually be attained absolutely, both are generally attempted at once.

Removal of the Poison.— The measures directed to this end must vary with the site to which the poison was applied.

On the skin and on accessible mucous membranes this will be accomplished by a thorough washing with water. This will also be useful by diluting the poison. If the poison is only sparingly soluble in water (as phenol) alcohol may be employed. Soap may be useful, but should be avoided if the poison is an alkali. The appropriate chemical antidote should also be added to the wash water (for acids or bromin: Soap or Linimentum Calcis; for alkalies: vinegar or lemon juice). The poisons which are important in these situations are all irritants, and the further treatment consists in the application of oils or salves. If the poison has been applied *hypodermically or to wounds*, the systemic effects may be lessened by preventing or retarding the absorption of the poison. The absorption can often be delayed sufficiently so that the drug is excreted as fast as it is absorbed, and doses which would otherwise be fatal may cause no effect. The best means for this purpose is a firm ligature applied centrally to the wound. Where this is not feasible, sucking, cautery, or excision may be resorted to.

If an irritant poison has been *taken by the mouth*, the oral cavity and the pharynx demand the same treatment as would the skin.

With **gaseous poisons,** the treatment consists in free ventilation of the lung, using artificial respiration, if necessary, and oxygen.

Removal from the Alimentary Canal.— This is always the first step in the treatment of a case of poisoning by mouth, unless the symptoms are already so far advanced as to make it useless. Even if the poison has been administered some time before the treatment is begun, or if it has been given hypodermically, the alimentary canal should be cleansed, since many poisons (notably morphin) are excreted by this channel, and then again reabsorbed. The only contraindications to the emptying of the alimentary canal are: extensive corrosion, and advanced strychnin poisoning. Great caution and careful judgment are required in these cases.

The measures for the removal of poisons from the alimentary canal consist in emptying the stomach and intestine. A *cathartic*, however, need only be administered after the acute manifestations are past. Oily cathartics should usually be avoided, and enemeta are useless. The best purgatives in poisoning are the cathartic salts (15 to 30 Gms. of Magnesium sulphate); if the poison is not an irritant, 0.01 Gm. of podophyllin may be added.

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[1] Exercises 14, 17, 18, 29.

Evacuation of the Stomach.— Vomiting often occurs spontaneously, but even in this case, more active measures are generally required. These consist in the administration of emetics, or in lavage.

Lavage always deserves the preference, if it can be used. It cleanses the stomach much more effectually, particularly of small insoluble adherent particles; it is less depressant to the patient; and it permits the convenient use of chemic antidotes. It is indispensable with depressant poisons which paralyze the vomiting center (such as deep morphin or chloral poisoning).

The complicated stomach pump has been generally abandoned for the more convenient stomach tube. In emergencies, six feet of soft rubber tubing, with a funnel attached, answers very well. The tube should not be *forced* down, but should be *gently* pushed to the pharynx, where the pharyngeal muscles will grasp it and push it further. Care should be taken to avoid overdistention of the stomach; it is much better to use small quantities of fluid frequently. If there is much pain, 0.05% to 0.1% of cocain may be added to the wash water. If there is trismus, or the patient resists, the tube may be passed through the nose.

Emetics have the advantage of greater convenience, and avoid struggling. They should be repeated every fifteen to thirty minutes, if necessary.

Apomorphin.— [5 mg. (grain $^1/_{10}$ in 1% solution = 0.5 c.c. or ♏ *x*] hypodermically. This is the only emetic which can be given by the skin, and is therefor particularly useful if the patient resists. It is very prompt and certain, but rather more depressing than the following emetics:

Copper Sulphate or Zinc Sulphate.— About 1 Gm. (a knife-pointful) in half a glass of water. These act promptly and with a minimum of depression, but should not be given if the poison is a corrosive.

Ipecac.— A teaspoonful of the powder in water, or a tablespoon of the wine. Uncertain, and produces considerable depression.

Mustard.— A teaspoonful stirred in a tumbler of warm water. This is the most uncertain of these emetics, but useful in emergencies.

Neutralization of the Poison — Chemical Antidotes.— The object of these is, to render the poison incapable of acting, or of being absorbed. They accomplish this by enveloping the poison with an impenetrable coating, or by precipitating it, or by destroying it. Since these antidotes are hindered in their action by the presence of food, and since the precipitates are not perfectly insoluble, it is well to combine them with lavage or emesis, adding the antidotes to the wash water, or giving them in the interval between vomiting; they must be repeated frequently.

Demulcents (raw eggs, acacia, boiled starch or flour, milk, ad libitum).— These act by lessening absorption; by allaying inflammation; and in the case of metals, by precipitation.

Precipitants.— The most universally applicable of all precipitants is *tannin* (a teaspoonful of tannic acid, or preferably, very strong hot tea, ad libitum). The efficiency will be increased by the addition of sodium acetate or bicarbonate, and diminished by alcohol and acids, since the precipitates are soluble in these media.

From the experiments of Kiefer (1892), on tannin, and Sollmann (1901), on tea, it may be deduced that these are *useful* against: Apomorphin, Cinchona alkaloids, Hydrastin, Strychnin, Veratrin, Digitalis, Antipyrin, Colchicin; and the metals: Pb, Ag, Al, Co, Cu, Ni, Ur, Zn, Fe.

Scarcely useful against: Cocain, Brucin, Aconitin, Lobelin, Nicotin, Pilocarpin, Codein, Muscarin, Physostigmin, Solanin.

Practically useless against: Atropin, Coniin, Morphin, As, Sb, Hg.

Of other, *specific precipitants,* the following should be remembered: For

Alkaloids.— Tincture or compound tincture of iodin, 15 drops in half a glass of water.

Metals (especially mercury).— Raw eggs.

Arsenic.— Arsenic antidote (see Index).

Barium.— Sulphates (Glauber's or Epsom salt).

Oxalates.— Calcium (limewater, chalk, whiting).

Phosphorus. Copper sulphate or Oxidized (old) Turpentine. (The former envelopes the phosphorus with an insoluble coating of metallic copper. Turpentine forms the insoluble turpentine-phosphoric acid.)

Antidotes Which Destroy the Poison in the Alimentary Canal.— (These, for the most part, will not be useful after the poison is absorbed.)

Acids.— Alkalies (burnt magnesia, soap, chalk, baking soda).

Alkalies.— Weak acids (vinegar, lemon juice).

Organic Poisons (Alkaloids, Glucosids, etc.) and Phosphorus.— Oxidizing agents, especially Potassium permanganate, 1 Gm. (one-third teaspoonful) in a pint of water. Care must be taken that no undissolved crystals are administered; H_2O_2. (In case of snake bite, the powdered permanganate may be rubbed into the wound, after free incision.)

Hydrocyanic Acid.— The above, also arsenic antidote, hydrogen peroxid, and hyposulphite of sodium.

Carbolic Acid.— Sodium sulphate; alcohol.

Antidotes Which Destroy Poisons After They Are Absorbed.— To be effective, these must be given hypodermically or intravenously. The best known examples of this class are the antitoxic sera. The following are also useful: Sodium hyposulphite against hydrocyanic acid; and sodium carbonate against mineral acids.

Removal of Poisons After Their Absorption.— This can be accomplished by increasing the excretions. The elimination by the alimentary canal has been discussed. The principal remaining channels are the urine and sweat, of which the former is by far the more important.

Diuretics.— Water, especially as weak tea or carbonated drinks; diuretin; potassium acetate (irritant diuretics should be avoided).

Diaphoretics.— Hot drinks; heat; pilocarpin (if not contraindicated by pulmonary edema). Diuresis and diaphoresis often fail, partly because they are too slow, partly because not all poisons are eliminated by these channels.

Infusion of Normal Saline Solution (1 Liter of 0.9% injected under the skin of the subclavicular region) increases elimination by all channels. *Bleeding* may be resorted to in some cases. Up to a liter of blood may be drawn, a double quantity of salt solution being injected.

Symptomatic Treatment.— The symptoms produced by poisons can often be lessened or removed by the use of drugs having an opposite action. It is not to be supposed that these *physiologic antidotes* really lessen the action of the poison, although they cover its symptoms. But by tiding the patient over the dangerous period, and by preventing exhaustion, they are often potent means of saving life. It must be remembered, however, that large doses of the antidotes often cause effects similar to those of the poison, which may add to the fatality of the latter. They must therefore be used in appropriate small doses.

It is not purposed to enter in this place into the special physiologic antidotes, but we shall take up only those measures which are generally useful.

These measures are directed, in the *order of their importance,* to: supporting the respiration, heart, and vasomotor tone; to lessen cooling, pain, and convulsions, and coma.[1]

Respiration.— This is usually the first function to fail, and accelerates the other actions of the poison through the convulsant and paralytic effects of asphyxia, and by preventing the destruction of poisons through oxidation. For these reasons, it is well not to wait with the supporting measures until the respiration has actually failed, but to begin as soon as it shows signs of weakening. The measures consist in direct or reflex stimulation of the respiratory center; in artificial respiration; and in the administration of oxygen.

Reflex stimulation of the respiratory center is the quickest, but can not be kept up as long as the direct stimulation. It may be secured by the administration of ammonia, by inhalation of ammonia water or smelling salts, or by aromatic spirits of ammonia (half a teaspoonful in a glass of water); the alternate application of heat and cold (whipping with wet towels); friction with alcohol, or camphorated oil: hypodermic injection of brandy, whiskey, or ether; mustard plasters.

Direct Stimulation of the Respiratory Center.— By strong hot coffee, strychnin (0.002 Gms.) or atropin (0.001 Gm.). The respiration may also be raised by improving the circulation. Saline infusion is also very effectual.

Artificial Respiration.— This should be resorted to whenever the above measures are ineffectual. Any of the commonly used methods (also rhythmical stimulation of the phrenic nerve) may be used. The mechanical distention of the lungs also seems to cause a reflex lowering of the excitability of the nerve centers, thereby lessening the tendency to fatigue in convulsant poisoning. It should be remembered that very prolonged and violent artificial respiration may injure the lungs. It should also be remembered that artificial respiration is apt to induce apnea, so that the patient does not breathe spontaneously simply because there is not enough CO_2 in the blood to stimulate the respiratory center. If the heart is strong, the artificial respiration should therefore be intermitted occasionally for a short time.

Oxygen.— This will be useful in every case of failing respiration, and particularly if an asphyxiant gas is the cause of the poisoning.

Heart.— It appears to be impossible to stimulate a poisoned heart directly. The best results are obtained by the injection of normal saline, possibly with the addition of some suprarenal alkaloid (1:100,000). Digitalis is usually unsuccessful. Strong rhythmical pressure (rate of 100 per minute) over the cardiac region of the chest, may be helpful. A fatigued heart can often be revived by lowering the blood pressure by alcohols or amyl nitrite, or by withdrawal of blood.

Vasomotor Stimulation.— This is usually accomplished by the reflex stimulants mentioned under respiration. Lowering of the head and bandaging the extremities is often sufficient.

Cooling.— This is prevented by the application of external heat; **Pain** by morphin, or if local, by cocain; **Convulsions** are controlled by the cautious inhalation of chloroform; **Coma** by reflex stimulants, coffee, and atropin.

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[1] Consult Exercise 48.

Methods of Administering Antidotes.— Physiological antidotes should be given hypodermically or intravenously, if possible. This obviates the loss of the antidote through vomiting, and the action is in every case more prompt and more certain. If the circulation is very low the absorption of hypodermic injections may also be very slow. It is therefore well to thoroughly massage the site of the injection, and if the circulation has almost stopped, to employ vigorous rapid rhythmical compression of the heart (this maintains a fairly efficient artificial circulation even after the heart has stopped beating).

RESUME OF THE GENERAL TREATMENT OF POISONING.

Promptness is of vital importance. The physician should be familiar with antidotes; he should have these antidotes readily accessible; he should plan his treatment on his way to the patient. If he finds the condition of the patient dangerous, he should at once proceed to relieve the symptoms. Otherwise he should first administer the chemical antidote and evacuate the stomach; apply heat; attend to the respiration, to pain, to any other symptoms; give a diuretic, and, finally, a cathartic.

Antidotes for First Aid.— Every physician (and every drug-store) should keep the following antidotes together, in a special satchel ("Antidote-Bag") so that they can be readily transported. The dose should be written on each container. Amyl nitrite pearls; Apomorphin tablets, 2 mg.; Atropin tablets, 1 mg.; Caffein Citrate; Chloroform; Cocain hydrochlorid tablets, 0.03 Gms. (2 to 4 per quart); Compound tincture iodin; Copper sulphate, powdered; Lime Water; Magnesia, calcined; Potassium permanganate, 1% solution (to be diluted ten times); Sodium sulphate; Spir. Ammon. Arom.; Strychnin sulphate tablets, 2 mg.; Whisky; also a hypodermic syringe in good order, and a stomach-tube with funnel.

The following should be demanded at the house of the patient: Boiled water; Coffee (strong, hot, and black); Eggs; Hotwater bags; Milk; Mustard; Salad oil; Salt; Soap; Starch, boiled; Tea, Vinegar.

CHAPTER VI.

PRESCRIPTION WRITING; FLAVORING.

(A) PRESCRIPTION WRITING.

Definitions.— A prescription is an order for medicine, sent by a physician to a pharmacist. It consists of the following parts (in this order):

1. *Superscription:* The heading (R).

2. *Inscription:* The ingredients and their amounts.
3. *Subscription:* The directions to the dispenser.
4. *Signature:* The directions to the patient.

The prescription should also bear the signature of the physician, the date, and the name of the patient.

The *Inscription* may consist of but one ingredient. If several are used, they should be placed in the following order:

Basis: the principal substance.

Adjuvant: the substance which is used to aid the action of the basis.

Corrective: whose purpose it is to modify or correct an undesirable action of the basis.

Vehicle: the indifferent substance used to dilute the active ingredients.

The inscription is always written in Latin, which has various advantages over English for this purpose:

In the first place, the names of the drugs are more definite, concise, and unchangeable. There is, as a rule, but one Latin name for each drug, whereas in English the same substance may have several names, or the same name may designate several entirely different substances. Further, it is often desirable to have the patient ignorant of what medicine he is taking. On the one hand, if he possesses this knowledge he very frequently has preconceived ideas of the action of the medicine, and will either take it in excessive amounts or will neglect to take it entirely, or interfere with its action in some other way. On the other hand, it will encourage the habit of self-medication.

The *directions to the dispenser* are generally written in Latin. There is, however, no necessity and no advantage in this. Usually it is sufficient for this purpose to write simply the letter M (misce) below the inscription.

The *directions to the patient* (signature) are always written in English, so that the patient can read them. The directions should be made as complete as possible, and should include everything which it is necessary for the patient to know. The habit of giving verbal instructions to patients and of having the medicine labeled "use as directed" cannot be too much discouraged. Aside from the fact that human memory is extremely apt to fail, the patient or relatives, when the prescription is given to them, are usually in a more or less excited frame of mind, and cannot be relied upon to remember what is told them. Medicines intended for external application should be plainly labeled to that effect, and when a medicine contains poison, it should be so labeled, except when there is special objection to this.

The custom of having prescriptions "*refilled*" obtains in many localities. Whereas it is often impossible for the physician to put a stop to this practice, it is absolutely necessary that he should prevent such prescriptions being refilled which contain narcotics or other drugs likely to cause a habit. He can attain this result by writing "*non repetatur*" under the prescription. The druggist refilling this will do so on his own responsibility.

When the patient is very poor, it is often customary to invite the druggist to charge him the lowest terms by writing *P. P.* (Pauperissimus) under the prescription. It is, of course, not just to do this if the physician himself receives a regular fee.

GENERAL HINTS ON PRESCRIPTION-WRITING.

General Hints.—The subject of prescription-writing seems to possess almost insurmountable difficulties for the student. There is, perhaps, no other subject in the whole course of study which he finds more discouraging and finishes with less satisfaction. Nevertheless the principles upon which it is based are few, simple, and easily memorized. When asked for them, the student usually has no difficulty in answering the questions. The difficulties appear when he tries to put these principles into practice. But it is the same with any other art: nothing but practice will give expertness. The student who would master this subject must not rest content with doing the few exercises which can be given him in class. As he studies each drug, or as he reads up the treatment of diseases, he should himself compile such prescriptions as the subject suggests. This will not only aid him in prescription writing, but in pharmacology and therapeutics as well. It is only in this way that he can acquire the necessary self-confidence and skill. In this home-practice, method and detail should be cultivated, for in these lies the secret of the art. The following rules may prove helpful:

When writing a prescription for a given condition, put down, first, the name of the best remedy. Ask yourself whether there is any other drug which may be employed to aid or usefully modify this. Put this down also. Then consider in which form the medicine should be administered, whether as liquid, powder, salve, etc.[1] This will usually determine which preparation of the ingredient is to be employed. Put this down also. Then ask yourself what may be added to render the mixture agreeable to the patient. When this is written, all the ingredients will be represented. Now look over these carefully and see that there are no incompatibilities and that the constituents are soluble if the mixture is to be a liquid. Write the directions to the dispenser. Assure yourself that the prescription is grammatically correct (especially the endings). Decide how many days the mixture is to be taken, and how many doses a day (on the basis of sixteen hours to the day). Decide whether the dose of the total mixture is to be a teaspoonful, tablespoonful, etc. By multiplying the total number of doses with the size of the single dose, ascertain the approximate size of the mixture. Round this off to a convenient figure.[2] Multiply the single dose of each ingredient by the total number of doses (again reducing the quantities to round numbers, unless the constituent is very active). Check the doses. Write the directions to the patient. Consider whether a *non-repetatur* is advisable. Affix your signature, the date, and the name of the patient. This finishes the prescription. Look over the result carefully in the same order.

It would seem almost superfluous to mention that it is extremely essential in writing prescriptions to use as *legible handwriting* as possible. It is astonishing, in view of the dire results that may follow, how often this self-evident rule is disregarded. The same remarks apply to *abbreviations*. While it is justifiable to employ abbreviations even extensively, it is necessary to make these in such a way that they cannot possibly be misinterpreted. This is learned best in class practice.[1]

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[1] If the medicine is intended for EXTERNAL USE, it may be prescribed as:
Plaster: If the action is to be prolonged and superficial.
Ointment: If the action is to be deeper.
Lotions or Injections, Eye-waters, Gargles, etc.: If it is soluble in water.
Liniment: If it is soluble in oil or alcohol.
If the medicine is to be used in INTERNALLY, it may be prescribed as:
Solution: If the ingredients are soluble in water, alcohol or glycerin.
Mixtures or Emulsions, i. e., suspended by acacia, if insoluble in water.
Powder: If the substance does not have a very bad taste. These are preferred to the following preparations if the dose is bulky, or if the substance is to be dissolved in water before swallowing.
Pills, Capsules, etc.: If the substances are solid or semisolid, and possess a disagreeable taste; or if they are to act locally on the alimentary canal.

[2] Fluids should be prescribed so as to approximately fill the bottles in current use (15, 30, 60, 125, 150, 200, 400 c. c.) (½, 1, 2; 4; 6; 8 and 16 ounces).

For drop doses and eye waters, the usual amount is 15 to 30 c. c. (½ to 1 ℥); for teaspoon doses, 30 to 125 c. c. (1 to 4 ℥); for gargles and injections, 60 to 150 c. c. (2 to 6 ℥); lotions, 120 to 200 c. c. (4 to 8 ℥); tablespoon doses, 150 to 400 c. c. (6 to 16 ℥). Pills are prescribed in numbers of 5 to 25; powders, 1 to 12; ointments, 10 to 30 Gms (½ to 1 ℥).

An efficient aid in acquiring practice in writing prescriptions is to look over a druggist's prescription file, when this may be done.

The copying of a prescription, ingredient for ingredient and dose for dose, is as much empiricism as the use of any other ready-made compound. The physician should be well enough educated to devise his own prescriptions and to select such ingredients as will best suit the special needs of the case in hand.

The following is the *type of a complete prescription:*

Superscription	R	Gm. vel. C.C.	
Inscription: Basis	Tincturæ Aconiti	0	45
Adjuvant	Spiritus Ætheris Nitrosi	15	
Corrective	Liquoris Ammonii Acetatis	15	
Vehicle	Elixiris Aromatici	30	
Subscription	Misce		
Signature	S. Teaspoonful every hour in half a glass of water. Dr. X................. Jan. 1, 1905. For Mr. Y...........		

Simplicity in Prescription Writing.— Formerly the ingredients of a prescription were almost numberless. This was in the time of empiricism, and was simply an application of the idea that in a large mixture of substances there would probably be one which would do good. This was the so-called "shot-gun prescription." At present the tendency in prescription writing is to make the prescription as simple as possible. This avoids the chances of incompatibilities, and, what is more important, makes the action of the medicine more easy to watch and control.

If the prescription includes a number of mixtures, each containing several ingredients, such as the numberless preparations now put on the market by many firms, the result is, of course, as much a "shot-gun" prescription as if the prescriber had enumerated all the ingredients.

Maximal Doses.— The pharmacist is supposed to check the quantities of the ingredients, and not to dispense a prescription containing an *unusual dose of a powerful poison* without convincing himself that the physician prescribed this intentionally. While this does not in any way lessen the responsibility of the physician, it is a safeguard which deserves all encouragement. To avoid delay, it is customary to mark such large doses in such a way that the pharmacist will have no doubt that they are intentional. Thus:

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[1] The author has found it very useful in class-practice in prescription writing, to make some of the students in turn work out the prescriptions on the blackboard, and to subject these to the criticism of the class.

Tr. aconiti, ʒj; or ʒj!; or ʒj Q. R. (quantum rectum), the last being the best.

The student should familiarize himself thoroughly with these "maximal doses," i. e., the largest doses which are ordinarily administered. These are given in the following table. The maximal dose should be used at most three times a day. The ordinary dose is generally one-fifth to one-half of the maximal.

TABLE VIII.—MAXIMAL SINGLE DOSES.[1]

	Gm.	Gr.		Gm.	Gr.
Atropin	0.001	1/64	Ant. Pot. Tart.	0.2	3
Scopolamin			Tr. Iodi		
Hyoscin			Fol. Digitalis		
Physostigmin			Colocynth	0.3	5
Digitoxin			Gamboge		
Phosphorus			Acetanilid	0.5	8
Arsenic Comp'ds.	0.005	1/12	Chloroform		
Elaterin			Bromoform		
Strychnin	0.01	1/7	Creosote		
Heroin			Liquid Arsenic Prepns.		
Pilocarpin	0.02	¼	Tr. Strophanthi		
Apomorphin			Copper Salts	1.0	15
Mercuric Salts			Zinc Salts		
Silver Salts			Caffein Citr.		
Morphin	0.03	⅓	Theobromin		
Ext. Nuc. Vom.	0.05	⅔	Phenacetin		
Cocain			Tr. Nuc. Vom.		
Ol. Tiglii			Pv. Ipec. et Opii	1.5	20
Phenol	0.1	1½	Tr. Digital (10%)		
Codein			Tr. Opii		
Plumbi Acet.			Tr. Aconiti (10%)		
Podophyllin			Sulfonal	2	30
Santonin			Vin. Colchici		
Ext. Cannabis Ind.					
Opium	0.15	2½	Chloral	3	45

Grammatic Construction of Prescriptions.—The heading, inscription, and often the subscription are written in Latin.

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[1] In the case of alkaloids, the dose applies to the salts, not to the free alkaloid.

A slight knowledge of the rules of grammar of this language is therefore essential. It is supposed that this is possessed by the student, and the following is intended merely to recall some of the more important facts:

The superscription, R (recipe: "take thou"), requires the name of the substance to be in the genitive, if the quantity is given, the quantity itself being in the accusative (the latter is, of course, very rarely written out in full). When the quantity is not given, the name of the substance is to be placed in the accusative. Adjectives agree with their nouns in gender, number, and case.

These rules will generally be understood by translating into English: *e. g.,* Take thou of tincture of aconite one ounce.

The following **rules for the formation of the genitive case** will be found valuable ("Mann's Manual"):

Rule 1.—*All nouns ending in* a, *form the genitive in* æ; as Quinina, Quininæ. *Exceptions:* Aspidosperma, Physostigma, and Theobroma form the genitive in atis. Folia is plural; genitive, foliorum.

Rule 2.—*All nouns ending in* us, um, os, on, *form the genitive in* i; as Conium, Conii. *Exceptions:* Rhus, gen. Rhois; Flos, gen. floris; Erigeron, gen. Erigerontis. Fructus, Cornus, Quercus, Spiritus, do not change.

Rule 3.—*All other nouns of whatever termination make the genitive in* s, *or* is. Elixir, gen. Elixiris.

Some lengthen the termination thus:

as, genitive	atis;	as Acetas,	Acetatis.
is, "	idis;	as Anthemis,	Anthemidis.
o, "	onis;	as Pepo,	Peponis.
x, "	cis;	as Cortex,	Corticis.

There are a few exceptions. Asclepias, gen. Asclepiadis; Mas, gen. Maris; Phosphis, Sulphis, etc., gen. itis; Mucilago, gen. Mucilaginis; Solidago, gen. Solidaginis; Pulvis, gen. Pulveris, etc.

The following words do not change in their genitive: Azedarach, Buchu, Cannabis, Catechu, Condurango, Cornus, Curare, Cusso, Fructus, Digitalis, Hydrastis, Jaborandi, Kino, Matico, Quercus, Sassafras, Sago, Sinapis, Spiritus, Gambir, Sumbul.

The **accusative** is rarely employed. It is formed according to the following rules (Mann):

Rule 1.—*Nouns singular ending in* a, *are feminine, and make the accusative singular in* am *and the plural in* as. Example: Drachma, acc. sing. Drachmam, pl. Drachmas.

RULE 2.— *Those ending in* um *or* us, *make the accusative singular in* um. *The accusative plural of those in* us *is* os, *and of those in* um *is* a. Those in *us* are masculine, those in *um* are neuter:

Congius, acc. sing. Congium; acc. pl. Congios.
Granum, acc. sing. Granum; acc. pl. Grana.

RULE 3.— *Those whose genitive ends in* is, *form the accusative in* em, *plural* es.

Attention is also called to the fact that adjectives change their endings, a fact which the student is apt to forget.

The directions to the dispenser are usually written in Latin, but this is not essential. They should, in every case, be as brief as possible. As a rule, the pharmacist is better informed as to this part than the prescribing physician.

The following *prepositions* are frequently used, and command the following cases:

ad	to	accusative.
ana	of each	genitive.
cum	with	ablative.
in	into	accusative.

The following **Latin words and phrases** occur frequently in prescriptions (adapted from Mann):

TABLE IX.

ad	to, up to
ad libitum	at pleasure
adde	add (thou)
ana (ā, āā)	of each
aqua bulliens	boiling water
" fontana	spring water
" fervens	hot water
" destillata	distilled water
bene	well
bis in dies	twice daily
cape, capiat	take, let him take
charta	a paper (medicated)
chartula	a small paper for a powder
cibus	food
cochleare magnum	a tablespoon
" parvum	a teaspoon
cola, colatus	strain, strained
collyrium	an eye wash
congius (C.)	a gallon
cum	with
dilute, dilutus	dilute (thou), diluted

dimidius	one-half
divide (Div.)	divide (thou)
dividendus	to be divided
dividatur in partes æquales	let it be divided into equal parts
dosis	a dose
extende supra	spread upon
fac, fiat, fiant (ft.)	make, let be made, let them be made
fac tales doses	make such doses
filtra	filter (thou)
gargarisma	a gargle
gutta, guttæ (gtt.)	a drop, drops
haustus	a draught
hora	an hour
hora somni	just before going to sleep
hora decubitus	at bed time
in dies	daily
instar	like (with genitive)
lac	milk
libra (lb.)	a Troy pound
mane primo	very early in the morning
magnus	large
misce (M.)	mix
more dictu	as directed
non repetatur	do not repeat
numerus, numero (No.)	a number, in number
octarius (O.)	a pint
ovum	an egg
pars	a part (governs genitive)
partes æquales (P. æ.)	equal parts
parvus	small
pilula (pil.)	a pill
pro re nata	according to circumstances, occasionally
pulvis	a powder
quantum sufficit (q. s.) (followed by genitive)	as much as is necessary
quaque hora	every hour
(cum) semisse (ss.)	and a half
signa	sign
sine	without
si opus sit	if necessary
solve, solutus	dissolve, dissolved
solutio	a solution
statim	immediately
talis	such
tritura	triturate
tere simul	rub together
ter in dies	three times a day
vitellus	the yolk (of an egg)

(B) FLAVORING.

I. GENERAL RULES.

The subject of flavoring is one which is very generally neglected by the beginning practitioner, and is one treated very slightly indeed in most text-books on materia medica. It is, however, one of very great importance with the modern patient. Attention to this on the part of manufacturers and the lack of it on the part of physicians is perhaps largely responsible for the increased use of proprietary medicines. Patients very often will fail to take a disagreeable medicine, and the physician should always be on the lookout for such cases. It is scarcely necessary to say that he should approximately control the amount taken by judging as to the quantity left in the container, as he should also, in general, control the medicine dispensed by the druggist as to its appearance and taste.

Some patients will carry the deceit somewhat further and pour away the appropriate amount of the medicine, and if the physician does not obtain the anticipated results, it may be well to prescribe some test medicine, such as salol (0.3 Gm.), or potassium iodid (0.5 Gm.), which can be detected in the urine (Exercise 13).

The subject of flavors is not only important because it humors the patient, but when the flavoring is properly done it has an advantageous action in the treatment of the disease. It puts the patient in more favorable condition for the action of the drug, aiding absorption and digestion. One need only point to the value of condiments in food. It is rather surprising that a physician who would object very strongly to eating his food without seasoning will prescribe medicine without giving a thought to this subject.

Condensed Rules.— The substances which may be used for improving the taste of a mixture are almost without number. Before proceeding to a detailed discussion, we shall give in a condensed form those methods which are apt to be most useful. The quantities need not necessarily be specified, it being sufficient to mark them "q. s."

Appearance.— Liquid prescriptions intended for internal administration should be clear if possible. It might be well to mark all such prescriptions "filtra." The appearance may be very materially improved by the addition of some coloring-matter, and this may also prove useful through its suggestive element and by hiding the nature of the medicine from the patient. The following are recommended for *solutions* in the proportion of about 2 drops to the ounce (0.4:100):

Red:	*Tinctura Persionis N. F.[1]
Brown:	*Tinctura Persionis Composita N. F.
Yellow:	*Tinctura Curcumæ N. F.

For *powders* Carmine.

For **improving the taste** for children, Syrupus Tolutanus; for *adults,* Elixir Aromaticum.

For the administration of *salts,* where the alcoholic elixirs are not admissible, use Aqua Menthæ Piperitæ or 2 grains of citric acid per ounce (0.4:100).

For *emulsions,* 6 drops Spiritus Aurantii Compositus per ounce (1:100); other flavoring spirits are used in the same proportion.

* Not official.

[1] U. S. P. = official in United States — B. P., in British Pharmacopœia; N. F. = National Formulary.

For producing a *bitter* flavor use Elixir Gentianæ N.F.

To render the administration of a great amount of *hot water* acceptable, use decoction of Species Pectorales N.F. in the proportion of 2 tablespoonfuls to the cup.

For the administration of *cold water* use lemonade.

For the flavoring of *cough medicines* use Syrupus Glycyrrhizæ.

II. DETAILS: COLORING.[1]

Anilin colors should be avoided as far as possible, since they are frequently more or less toxic.

1. Watery or Alcoholic Liquids.

The following are especially useful in slightly acid liquids. The tinctures are used in the proportion of 2 drops to the ounce (0.4 : 100).

(*A*) *To produce a* **red color:**

* *Tr. Persionis* N. F., prepared from a lichen — 12½% — one-third alcohol — miscible with alcohol and water.

(*B*) *To produce a* **reddish-brown color:**

* *Tr. Persionis Comp.* N. F.— 2% persionis, 10% caramel — miscible with water and alcohol.

(*C*) *To produce a* **yellow color:**

* *Tr. Curcumæ* N. F. (Curcuma longa, Turmeric, Zingiberaceæ, Southern Asia) — 15%, alcohol, miscible with alcohol, but not with water. If the mixture is aqueous, it must be filtered. Alkalies will change the color to reddish-brown.

Crocus, Saffron (Stigmata of Crocus sativus, Irideæ, cultivated in Spain and France).

It also contains volatile oil and is used popularly as a carminative and emmenagog.

Tr. Croci B. P., U. S. P.— 10% — one-half alcohol — miscible with water and alcohol.

(*D*) *To produce a* **brown color:**

Caramel — partly carbonized sugar.

(*E*) *For* **other colors,** anilin dyes must be used.

For blue, methylene-blue.

For violet, gentian-violet.

2. Oily Liquids.

(A) **Red:** * *Alkanet* — root of Alkanna tinctoria, Boragineæ — West Asia. (Red with acids; blue with alkalies.)

* *Madder:* Wood of Rubia tinctorum, Rubiaceæ. Levant and Southern Europe. Contains especially alizarin, and other coloring-matters. Little soluble in water.

(B) **Yellow:** * *Annatto* — pulp surrounding seeds of Bixa orallana, Bixineæ — South America — insoluble in water — soluble in alcohol, ether, and oil. (Frequently used for coloring butter.)

3. Powders.

(A) **Red:** * *Carmine* — a precipitate obtained from decoction of cochineal by alum or cream of tartar. Soluble in alkalies, brightened and precipitated by acids. Also soluble in alcohol. Contains carminic acid. May also be used for coloring liquids: * *Liquor Carmini* N. F. 6%, with ammonia and one-third glycerin.

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* Not official.

[1] The most important preparations are mentioned in the Lists of the Appendix (A.) Only these, and the data asked for, should be studied. The others are for reference, and need only be glanced over.
Study *Materia Medica Lesson 1.*

Cochineal U. S. P.— females of the insect Coccus cacti — Mexico and Central America.

Iron oxid or *carbonate.*

* *Armenian bole* is an iron-containing clay used for this purpose.

(B) **Blue:** * *Ultramarine* — compound of aluminium and sodium silicate and sodium polysulphid. It is insoluble.

* *Litmus,* a pigment obtained from lichens. Insoluble in alcohol, soluble in water.

* *Indigo,* a pigment obtainable from a number of plants and also synthetically. The active principle is a colorless glucosid, plant indican. Under the action of ferments or acids it yields indigo-blue or indigotin. This is insoluble in ordinary solvents, but dissolves in concentrated H_2SO_4. If this solution is neutralized with NaOH, the pigment remains in solution and produces a beautiful blue color, which is, however, destroyed by oxidizing or reducing agents.

(C) **Black:** * Lampblack or soot (fuligo ligni).

III. DISGUISING THE TASTE IN SOLID FORM.

This may be accomplished by administering the substance in the form of pills, triturates, capsules, cachets, tablets, etc. In the case of the ordinary pills or tablets, there is generally some taste before they can be swallowed, and this is obviated by coating them with gelatin, sugar, chocolate, etc. All these measures diminish the solubility of the substance, the most, perhaps, in the case of pills. Triturates or compressed tablets can be prepared so as to disintegrate and dissolve as easily as the powder itself. However, most of the preparations put out by the manufacturers do not conform to this demand, and probably all harden on keeping.

IV. MEASURES FOR DESTROYING THE TASTE.

Certain substances have the property of paralyzing the sensory endings of taste. Among these is Yerba santa. (See Chap. X.) This destroys the taste for bitter substances especially. It is, however, therapeutically objectionable. It probably renders alkaloids insoluble, and as for ordinary bitters, it is extremely probable that the therapeutic action is connected with the bitter taste. One c. c. of the fluid extract covers the taste of 0.012 Gm. of quinin sulphate or 1.5 Gm. of quassia.

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* Not official.

Study Materia Medica Lesson 1 and Exercise 3, IX.

Similar properties are found in the following plants:

* Gymnema sylvestre,— Africa.
* Bulmenia dulcifica,— Sudan.
* Phrynium Danielli,— West Africa.

The same object, the rendering tasteless of the substance, may be attained by rendering it insoluble in the saliva. This can be accomplished with a number of alkaloids by the addition of tannin. Unfortunately this almost invariably diminishes the solubility in the lower portions of the alimentary canal as well.

V. DEMULCENTS.

Demulcents may be defined as non-absorbable, slimy, colloid substances, generally soluble in water and insoluble in alcohol. They very markedly diminish the characteristic taste of all substances, acid, salt, and sweet, as well as bitter.

They do this by enveloping the substance and forming a protective layer over the mucous membrane, and in this way preventing the access of the substance to the taste organs. This, of course, diminishes absorption as well as taste. One can very readily convince himself of this "corrective" action by mixing a 1% solution of citric acid with water and with a thin starch paste. The latter will taste very much less sour. Colloid substances of this kind are present in fruits as pectin bodies, and have a very marked influence upon their taste. The raspberry, for instance, actually contains more acid than the currant and but little more sugar, its less sour taste being due to the greater amount of these pectin substances present in it.

The Materia Medica of the demulcents is contained in Chapter XXXI A.

VI. SACCHARINE FLAVORS.

The taste of many substances is disguised or rendered more acceptable by sweetening. Sugar (cane or beet) or its solution — syrup — is most commonly used. Honey, glycyrrhiza, saccharum lactis, glycerin, or saccharin are sometimes substituted. The flavored syrups are usually preferred, *e. g.*, Syr. Glycyrrhizæ, Aurantii, Acidi Citrici, Tolutanus, etc.; or Elixir Aromaticum or Adjuvans.

In cases where sweetening is desired and sugar is excluded, particularly in cases of diabetes, the artificial synthetic product *saccharin* may be substituted. It is about three hundred times as sweet as sugar, but the taste is not exactly the same. The dose for a cup of coffee or tea is about one-half to one grain. *Glycerin* is another sweetening substance which does not contain sugar, and is sometimes employed in place of saccharin. A principle of quite a different kind is the principle of *glycyerrhiza.* This acts only in alkaline liquids, especially ammoniacal. It has no taste if the liquid is made acid.

Saccharum, U. S. P. (Saccharum purificatum, B. P.) — used in the granulated form (beet- or cane-sugar may be used indifferently). It is very widely distributed in the vegetable kingdom. Soluble in 0.5 parts of water or 175 parts alcohol.

Syrupus (U. S. P.).— 85 Gm. in 100 c. c.; made by heat or percolation.

Honey (Mel Depuratum, U. S. P.) is also a very pleasant flavor when fresh and pure.

Of semi-solid preparations, the thicker are called *confections* (Confectio Rosæ). Powders may be incorporated in these, but they are largely obsolete. Somewhat thinner preparations were called *electuaries.*

Lump-sugar is useful for administering liquids given in drop doses. When flavored with an essential oil, it is called *eleosaccharum.*

Maple-sugar — the evaporated sap of Acer saccharinum, Aceraceæ, North America — may be looked upon as a natural eleosaccharum.

Other sugars — glucose, molasses, manna, maltose, etc. — are of small importance as flavors.

* **Glucose.**— Prepared by acting on corn-starch with hot dilute sulphuric acid, and found in commerce either as a syrup or in solid masses. It is not as sweet as sugar, and generally contains dextrin, which makes it less easily absorbed. It is less soluble than cane-sugar in water, but more so in alcohol.

Technically the term glucose is restricted to the syrup (in which the hydration is less complete) and grape-sugar to the solid. The commercial products are often contaminated with barium and sometimes even with arsenic, and are therefor harmful.

Saccharum Lactis (Milk-Sugar); *Manna; Glycerinum; Levulose:* see Index.

Benzosulphinidum (U. S. P.) [*Glusidum,* B. P.] (*Saccharin, Dulcin*).— A number of benzol derivatives have intense sweetening power. The official is the anhydrid of ortho-sulphamid-benzoic acid, $C_6H_4.SO_2.CO.NH$. A white crystalline powder, soluble in 250 water, 25 alcohol. About 500 times the sweetening power of sugar.

It has the properties of the coal-tar group and is therefor antiseptic and irritant. It is sometimes given in fermentative dyspepsia (0.1 to 0.3 Gms.) (0.2 Gm. = 3 grs., U. S. P.) Its long continued use interferes with digestion and may lead to nephritis. For sweetening the above dose should not be exceeded.

Glycyrrhiza, U. S. P. (*Glycyrrhizæ radix,* B. P.).— *Licorice.*— Root of Glycyrrhiza glabra, Leguminosæ. Southern Europe and western Asia. Its taste is especially agreeable to children; less so to adults. It is also demulcent. Contains:

Glycyrrhizin (a glucosid, the ammonium salt of which causes the taste); sugar, starch.

Preparations:

Extractum G.— The watery extract evaporated to a solid consistency (and usually formed into rolls). Soluble in water.

Fluidextractum G.— One-third alcohol and 5% ammonia water. Miscible with water and alcohol. Dose ad libitum (2 c. c. = 30 ♏, U. S. P.).

* *Syrupus G.,* N. F., *Elixir G.,* N. F., *Elixir G. aromaticum.*— 12% solid extract.

Glycyrrhizinum Ammoniatum, U. S. P.— Prepared by precipitating an aqueous alkaline extract by sulphuric acid, dissolving in ammonia, and evaporating the solution. Soluble in water or alcohol. It possesses no advantage over the extract, and is devoid of the demulcent properties. Dose, 0.3 to 0.6 Gm. (5 to 10 grains).

VII. FLAVORS PROPER.

These consist for the most part of essential oils, acting at once upon the organs of taste and smell. Sometimes, however, other solid constituents form the flavoring principle.

Essential oils act partly as reflex stimulants, and in that connection they will again be considered in Chapter XXIX. They consist of a

* Not official.

solid and a liquid portion (stearoptene and eleoptene), the latter being the stronger. They are soluble in alcohol and in ether, and only to an extremely small extent in water, but sufficiently so to impart their flavor to it.

These oils are prepared by distillation *per se*, with water, or by expression, or by solution with appropriate solvents, or by absorbing them with fixed oils. They are preferred to preparations made directly from the drug, since they are free from other extractive mateial. The essential oils lose their flavors very readily on keeping through the development of ozone, etc. Their keeping quality may be very much improved by adding to them three volumes of alcohol and using a correspondingly larger amount in the preparations. They may be divided into sweetish and aromatic flavors. To these may be added the acid flavors, and those belonging to miscellaneous groups having other therapeutic qualities.

Table of Materia Medica of Plants Containing Odorous Flavoring Principles.

(A) Sweet Flavors.

I. Rose Flavors.

NAME.	FAMILY.	HABITAT.	ACTIVE PRINCIPLE.
[1] _Rosa damascena_.....	Rosaceæ.	Southern Europe and Turkey; cultivated.	Oil of rose (ottar of rose).
" (other species)	"	Cultivated.	Volatile oil.
[2] _Fruits_............	"	"	Volatile oils and ethers.
*_Pelargonium_	Geraniaceæ.	"	Oil of rose geranium.
*_Andropogon nardus_.	Gramineæ.	East India.	Oil of lemon grass.
*_Andropogon Schoenanthus_.....	"	" "	Oil of Indian geranium.
*_Rosmarinus officinalis_	Labiatæ.	Cultivated.	Oil of rosemary.

II. Other Flowers.

(Often including the plant.)

NAME.	FAMILY.	HABITAT.	PART USED.	ACTIVE PRINCIPLE.
Lavandula vera......	Labiatæ.	Southern Europe; cultivated.	Flowers.	Oil of lavender.
*_Melissa officinalis_...	"	Southern Europe; cultivated.	Plant.	Oil of balm. Bitter principle.
*_Monarda punctata_..	"	North America.	"	Oil. (Horsemint.)
*_Trifolium_ (species) .	Leguminosæ.	North America.	"	Oil. (Clover.)
*_Melilotus officinalis_.	"	North America.		Oil. (Sweet Clover.)

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[1] Rose Oil. The eleoptene is the most valuable part.

[2] The greater number of the common fruits are obtained from plants of the family of Rosaceæ. Fruit jellys are useful to disguise the taste of pills, etc.

* Not official.

Study Materia Medica Lesson 2.

NAME.	FAMILY.	HABITAT.	PART USED.	ACTIVE PRINCIPLE.
**Citrus aurantium*...	Rutaceæ.	Cultivated.	Flowers.	Oil of Orange flowers (oil of neroli).
**Spiræa tomentosa*...	Rosaceæ.	North America.	Plant.	Oil. (Hardhack.)
**Iris florentina*.......	Irideæ.	Northern Italy; cultivated.	Root.	Oil and bitter principle. (Orris.)
Anthemis nobilis....	Compositæ.	Temperate zone.	Chamomile flowers.	Oil. Bitter.
**Sambucus* (species)	Caprifoliaceæ.	Temperate zone.	Elder flowers.	Oil. Gum.
**Tilia* (species).....	Tiliaceæ.	Temperate zone.	Linden flowers.	“ Gum.
Salvia officinalis....	Labiatæ.	Temperate zone.	Sage herb	“ Tannin.

III. Solid Odorous Principles.

NAME.	FRUIT.	FAMILY.	HABITAT.	PART USED.	ACTIVE PRINCIPLE.
[1] *Vanilla planifolia*....	Vanilla bean...	Orchidaceæ.	Central America.	Fruit.	Vanillin.
[2] **Dipterix odorata*.....	Tonka bean...	Leguminosæ.	Guiana.	Fruit.	Coumarin.

IV. Odorous Resins (Balsams and Gum-resins).

These usually contain benzoic or cinnamomic acid with volatile oils. They are slightly antiseptic and locally stimulant.

1. GUM-RESINS (emulsifying when rubbed with water):

NAME.	SOURCE.	FAMILY.	HABITAT.
Galbanum	Ferula Galbanum.	Umbelliferæ.	Persia.
**Ammoniacum*...	Dorema Ammoniacum.	“	“
**Olibanum*...... (Frankincense)	Boswellia.	Burseraceæ.	Africa and Arabia.
Myrrha	Commiphora Myrrha.	“	Africa and Arabia.

2. BALSAMIC RESINS (insoluble in water, soluble in alcohol or ether):

NAME.	SOURCE.	FAMILY.	HABITAT.
Benzoinum	Styrax benzoin.	Styraceæ.	Sumatra and Java.
Balsamum peruvianum..	Toluifera pereiræ.	Leguminosæ.	Central America.
Balsamum tolutanum....	“ balsamum.	“	Venezuela.
**Liquidamber* ... (Sweet gum)	Liquidamber styraciflua.	Hamamelideæ.	North and Central America.

* Not official.

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[1] VANILLA. The freshly collected bean has no flavor; this is developed by fermentation, by which a principle, coniferin, is changed into *vanillin* by the action of hydrolyzing and oxidizing ferments. The *vanillin*, an aldchyd, can also be obtained synthetically. It is official.

[2] Vanilla flavoring is often falsified with *tonka bean*.

NAME.	SOURCE.	FAMILY.	HABITAT.
Styrax	Liquidamber orientalis.	Hamamelideæ.	Asia Minor.
**Populus* (Balm of Gilead)	Poplar buds are covered with a balsamic resin.		

V. Musk Flavors.

MOSCHUS, musk, the dried secretion of the preputial follicles of Moschus moschiferus, Thibet and China.

The odor of the tincture improves on keeping. Also possesses in high degree the property, common to all odorous oils, of reflexly stimulating the medulla. A synthetic substance of similar odor ("artificial musk") is used in perfumery.

Some other animals yield similar products which are used in perfuming, but are of no importance in medicine. The same holds true of the synthetic substitutes.

Amongst plants, the Sumbul also shows a similar odor.

* CASTOREM. From the preputial follicles of Castor Fiber.

(B) Aromatic Flavors.

I. Orange Flavors.

The volatile oil is contained in large cells of the rind of the fruit. The plants all belong to the family Rutaceæ, and are cultivated along the Mediterranean and in Florida and California. Citrus vulgaris also contains a bitter principle.

NAME.	PRODUCT.
Citrus vulgaris.	Oleum Aurantii Amari (Bitter Orange).
" *Aurantium.*	" " dulcis (Sweet Orange).
" *Limonum.*	" Limonis (Lemon).
" *Bergamia.*	* " Bergamottæ (Bergamot).

II. Menthol and Similar Flavors.

The stearoptene of the oil is menthol or thymol. The whole plant is used.

NAME.	COMMON NAME.	FAMILY.	HABITAT.
Mentha piperita	Peppermint.	Labiatæ.	North America, etc.
" *viridis*	Spearmint.	"	" " "
" (other species)			
**Thymus vulgaris*	Thyme.	Labiatæ.	Cultivated.

III. Flavors from Umbelliferæ.

The oils are contained principally in the seed or root. The plants grow in temperate climates and are largely cultivated.

SEEDS: *Carum Carvi.* Caraway.
* " *Petroselinum.* Parsley.
**Apium graveolens.* Celery.
Pimpinella Anisum. Anise.
Anethum Fœniculum. Fennel.
* " *graveolens.* Dill.
Coriandrum sativum. Coriander.
**Daucus Carota.* Carrot.
**Cuminum Cyminum.* Cumin

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* Not official.

Study Materia Medica Lesson 1.

Roots: **Angelica purpurea.* Angelica.
**Archangelica officinalis.* "
**Osmorrhiza longistylis.* Sweet Cicely.

**Illicium verum* (star anise, family Magnoliaceæ) resembles anise greatly in flavor; other genera of the family (Magnolia acuminata) also possess very aromatic fruits.

IV. Other Sweet Aromatics.

NAME.	COMMON NAME.	FAMILY.	HABITAT.	PART USED.
Sassafras officinalis	Sassafras.	Lauraceæ.	North America.	Root bark (other portions of the plant also contain the oil).
Acorus Calamus	Sweet flag.	Araceæ.	North America.	Root.
**Aralia quinquefolia*	Ginseng.	Araliaceæ.	North America.	"

(Other species also contain similar principles. This drug is highly valued by the Chinese.)

NAME.	COMMON NAME.	FAMILY.	HABITAT.	PART USED.
**Trigonella Fœnum Græcum*	Fenugreek.	Leguminosæ.	India, Mediterranean; cultivated.	Seeds

V. Pungent Volatile Oils and Resins.

NAME.	COMMON NAME.	FAMILY.	HABITAT.	PART USED.
[1]*Gaultheria procumbens*	Wintergreen.	Ericaceæ.	North America.	Herb.
Caryophyllum	Cloves. Unexpanded flowers of Eugenia caryophyllata.	Myrtaceæ.	Tropics; cultivated.	
Pimenta officinalis	Allspice.	Myrtaceæ.	Tropical America; cultivated.	Fruit.
Cinnamomum Zeylanicum, or	(Saigonicum, * Cassia)	Lauraceæ.	China or Ceylon.	Bark.
Myristica fragrans	Nutmeg (Myristica) = seed; *mace (macis) = seed envelope (arillode).	Myristicaceæ.	Cultivated in tropical countries.	
Piper nigrum	Black pepper.	Piperaceæ.	India; cultivated in tropics.	Unripe seed.

(Piper album is the above peeled.)

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[1] The oil is methyl salicylate, and in larger doses shares the therapeutic properties of salicylic acid. *Oleum Betulæ* (Sweet Birch) also consists of methyl salicylate.

* Not official.

Study Materia Medica Lesson 2.

NAME.	COMMON NAME.	FAMILY.	HABITAT.	PART USED.
Elettaria Cardamomum	Cardamon.	Zingiberaceæ.	India; cultivated.	Fruit.
[1] *Zingiber officinale*	Ginger.	Zingiberaceæ.	Tropics; cultivated.	Rhizome.
**Asarum canadense*	Wild ginger.	Aristolochiaceæ.	North America.	Root.
Capsicum fastigiatum	Red pepper.	Solanaceæ.	Cultivated in tropical countries.	Fruit.

VI. Hydrocyanic Acid Flavors.

These are contained in the kernels, leaves, and bark of many plants of the rose family.

Of some importance are:

Amygdala amara (U. S. P.). *Bitter almonds.* The seeds of Amyg. Am., family Amygdalaceæ. Cultivated. The oil is chiefly benzaldehyd, C_7H_6O, with a little HCN. *Nitrobenzol* has a very similar odor.

Prunus serotina (*Prunus Virginiana,* U. S. P.). Wild cherry bark. (Tannin.)

Prunus laurocerasus (B. P.). Cherry laurel leaves.

Study Materia Medica Lesson 2.

(C) Preparations of the Foregoing.

All the plants may be used in the form of *decoction* or *infusion,* employing the usual strength of 1 : 20.

1. *Volatile Oils,* official. Used for flavoring in proportion of 1 drop to the ounce (0.2 : 100), but *only in alcoholic liquids* (they should be preserved diluted with 3 volumes of alcohol):

Oleum Amygdalæ Amaræ, U. S. P.
Anethi, B. P.
Anisi, B. P., U. S. P.
Anthemidis, B. P.
Aurantii Corticis, U. S. P.
* “ Florum.
Bergamottæ.
Betulæ, U. S. P.
Cari, U. S. P., B. P.
Caryophylli, U. S. P., B. P.
Cinnamomi, U. S. P., B. P.
Coriandri, U. S. P., B. P.
Fœniculi, U. S. P.
Gaultheriæ, U. S. P.

Oleum Lavandulæ Florum, U. S. P., B. P.
Limonis, U. S. P., B. P.
Menthæ Piperitæ, U. S. P., B. P.
Menthæ Viridis, U. S. P., B. P.
Myrciæ.
Myristicæ, U. S. P., B. P.
Pimentæ, U. S. P., B. P.
Rosæ, U. S. P., B. P.
Rosmarini, U. S. P., B. P.
Sassafras, U. S. P.
Thymi, U. S. P.

The following isolated flavoring constituents are also official: *Benzaldehyd* (Bitter Almonds); *Cinnaldehyd* (Cinnamom); *Eugenol* (Cloves); *Safrol* (Sassafras); *Vanillin* (Vanilla).

2. *Oleoresina.* (Not used for flavoring; strongly irritant.)

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[1] Several varieties are on the market. Besides the volatile oil, it contains resin, starch, and mucilage.

* Not official.

Study Materia Medica Lesson 3.

3. *Aquæ.* (Dose of the flavoring waters is ad libitum.)
(Official in both Pharmacopœias:)

Aqua Amygdalæ Amaræ.
Anisi.
Aurantii Florum.
" " Fortior.
Cinnamomi.
Aqua Fœniculi.
Mentha Piperitæ.
" Viridis.
Rosæ.
" Fortior.

4. *Spirits.* (Only miscible with alcoholic liquids; for flavoring, 10 drops to ʒ, 2 : 100.)

The following are official in the U. S. P.:

Spiritus Amygdalæ Amaræ.
Anisi (also B. P.).
Aurantii *Compositus* (blended aromatics).
Cinnamomi (also B. P.).
Spiritus Gaultheriæ.
Lavandulæ (also B. P.).
Mentha Piperitæ (also B. P.).
Mentha Viridis.

5. *Elixirs.* Miscible with water and alcohol. The aromatics are blended in the proper proportions. Dose ad libitum. The following are purely for flavoring:

Official:

Elixir Aromaticum.
Elixir Adjuvans (contains licorice).

National Formulary: Elixir Gentianæ.[1]

6. *Tinctures.* Dose, 10 drops to ʒ (1 : 50).

Official in U. S. P.:[2]

Miscible only with alcohol, not with water:
Tinctura Aurantii Amari.
Aurantii Dulcis (B. P.).
Benzoini.
Limonis Corticis.
Myrrhæ.
Tolutana.
Zingiberis (B. P.).

Miscible with water and alcohol:
Tinctura Cardamomi Comp. (B. P.).
Cinnamomi.
Gentianæ Comp.
Lavandulæ Comp.[3]
Moschi.
Vanillæ.

The compound tinctures contain other aromatics.

7. *Sydups.*[2] Dose ad libitum.

Official in U. S. P.:

Syrupus Acidi Citrici.
Amygdalæ.
Aromaticus (B. P.).
Aurantii (B. P.).
" Florum (B. P.).
Limonis (B. P.).
Syrupus Picis Liquidæ.
Pruni Virginianæ (B. P.).
Rosæ (B. P.).
Sarsaparillæ Comp.
Tolutanus.
Zingiberis (B. P.).

National Formulary:

Syrupus Coffeæ.
Cinnamomi.
Syrupus Glycyrrhizæ.

8. *Honeys.*

Official:

Mel Rosæ, U. S. P. Boracis; Oxymel.; Oxymel Scillæ, B. P.

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[1] This is detannated and may be used where iron is to be administered in combination with a bitter.

[2] Those marked (B.P.) are also official in the British Pharmacopœia.

[3] Also called Compound Spirit of Lavender.

Study Materia Medica Lesson 3.

9. *Confections.*

Official:

Confectio Rosæ, U. S. P. Piperis, Rosæ Gallicæ, Sennæ, Sulphuris, B. P.

10 *Species.*

National Formulary:

Species pectorales: contains Althæa, Tussilago, Glycyrrhiza, Anise, Mullein, Orris. Infusion made 1 : 10. Dose, teacup.

(D) Acid Flavors.

These are among the most useful for disguising an unpleasant taste. They also aid in dissolving such substances as alkaloids, and assist the absorption of liquids.

A larger amount of cold water can be taken and disposed of when it is used in the form of lemonade or as soda-water — *i. e.,* water saturated with CO_2. The latter acid and organic acids, especially citric, are the most useful. The mineral acids should not be employed, since they are liable to cause gastritis if their use is continued. *Carbonic acid* is useful especially for the administration of salts, and is most conveniently used in the form of granular effervescent salts. *Citric acid* is used in the proportion of 2 grains to the ounce (0.4 : 100), or it may be employed in the form of Syrupus Acidi Citrici (1%, flavored with lemon).

Tartaric acid may be used in the same proportion.

(E) Miscellaneous Flavors belonging to Other Groups.

1. *Caffein Flavors.*— These are discussed in Chapter VIII (B).
2. *Alcohol Flavors.*— Discussed in Chapter XIX (B).
3. *Bitter Flavors.*— These are especially agreeable to men and disagreeable to women and children. The active part are alkaloids, glucosids, or other unclassified "bitter principles." They are most often given for their physiologic effect and will receive more extended notice in Chapter XXX (A). As flavors, they are best combined with strong aromatics (Tinctura Gentianæ Composita).

Study Materia Medica Lesson 4.

PHARMACOLOGY, THERAPEUTICS, AND MATERIA MEDICA.

PART II.

PHARMACOLOGY, THERAPEUTICS, AND MATERIA MEDICA.

CHAPTER VII.

INTRODUCTION TO PHARMACODYNAMICS.[1]

From the definitions in the opening chapter it will be seen that the term "pharmacology," in its broadest interpretation, covers a very wide field — coextensive with all medical, and indeed with all natural science. In practice, the science of pharmacology cannot, of course, enter in detail into all the subjects with which it is more or less closely related; these are taught separately, forming a preparation for, or application of, the subject of pharmacology proper. The **relations of pharmacology,** however, should be kept in view. Its connection with other sciences is indeed very intimate. This may be seen, firstly, in its *methods,* which are only modifications of those employed in other research. For its intelligent study it requires as a preliminary a knowledge of the anatomy, histology, chemistry, and physiology of the living body, normal and as altered by disease, as well as of the chemic structure of the modifying substances (medicines).

It is related in particular to *chemistry,* in that it deals with chemic substances; in that the composition of these often gives valuable clues to their actions; and, further, in that all pharmacologic actions rest on a chemic basis; they are, in fact, reactions between the reagent and the living protoplasm.

It is related to *physiology,* and through it to *histology* and *anatomy,* in that it studies the modifications produced in physiologic processes and structures by pharmacologic reagents.

It is related to *pathology* and *clinical medicine,* since its utilitarian aim is to reduce pathologic processes to the physiologic. Unless the former are well understood, it is, of course, impossible to apply a rational remedy.

On the other hand, pharmacology, treated simply as a biologic science, has given valuable aid to all of these branches. It has aided medicine, in that it alone made rational therapeutics a possibility; pathology, in throwing light upon pathologic processes, such as, for instance, the infectious diseases. It is a frequent aid in physiologic investigation, poisons serving to stimulate or paralyze structures inaccessible to the scalpel or electrodes. It has also been used in histology: The action of atropin is one of the most ready methods of differentiating between striped and unstriped muscles. In chemistry pharmacologic action has even been used to aid in the determination of doubtful constitutional formulas.

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[1] Exercises 24 to 28.

It has in recent years been shown that many processes of the normal and pathologic organism are dependent upon what are strictly pharmacologic actions. We need only mention animal extracts, toxins, antitoxins, coma diabeticum, etc.; and the end of this tendency has not yet been reached.

It is, of course, impossible to avoid a certain amount of overlapping of these sciences, but in view of the importance of the subjects, it will be no disadvantage to have them presented from several points of view.

In the strict limits of the definition, pharmacology is only one branch of biology. It treats simply of a number of scientific facts without occupying itself with the practical deductions which may be drawn from these. The effects of the rarest chemical upon the rarest form of fern are as important to it as is the action of digitalis in cardiac disease. But since we will not study it as an abstract science, but as a part of medicine, we shall lay stress principally upon its practical application. It is none the less impossible to give a good knowledge of the subject, even from a practical standpoint, without taking up some substances which are not of present importance, either as medicines or as poisons, for the list of these is constantly changing. Just as every physician has his own materia medica, so has every country, every generation, every year.

It must also be remembered that this book is intended for study as much as for reference, and, consequently, such effects as are obtained from a large number of drugs are studied more particularly on those drugs in which the action is most characteristic, even if these drugs should not be so widely known.

The study of a large science, like the present, may be undertaken by studying first the general principles which it involves; and then applying these to details; or the details may be mastered first and made the basis for the deduction of the principles. Either method has its advantages and drawbacks. The proper way would seem to be to carry on the two at once. The present chapter will give some of the general principles, which apply to every drug. The student must not expect that he will understand these fully at the first reading; their full meaning will come to him only as he proceeds further in his studies. Until then, they may seem to him dry and uninteresting details. However, the more faithfully he works his way through the beginnings of the subject, the richer will be his reward in the end, the better his understanding of the facts, theories, and applications of pharmacology.

The Nature of Pharmacologic Action.— The living cell may be considered as a very complex laboratory, where chemic decompositions and syntheses, reductions and oxidations, etc., are constantly going on. These chemic changes lead to transformations of energy which find their final expression in the phenomena of life. The vital manifestations of the cell are therefore inseparably connected with physico-chemic transformations, which require for their occurrence the existence of certain chemic and physical conditions. The chemic essentials are: the presence of substances capable of liberating energy, and the conditions suitable for their reactions, such as a proper temperature, alkalinity, presence of ferments, etc. The physical conditions of life are: A viscid medium, containing colloid proteids, salts, fats, and water. It is evident that pharmacologic agents must act by modifying the chemic composition or the physical properties, of the cells; their action must be physical or chemic.

The **physical effects** consist principally in solidification, precipitation, or solution of cell constituents. The most important effect is on the proteid, and is produced by the metals, acids, or alkalies (formation of albuminates); by the coal-tar products, alcohol, neutral salts, or water (dehydration or hydration); by the electric charges borne by ions, etc.; as also by strictly physical conditions, such as heat, light, electricity, etc. Solution or removal of the fatty constituents of cells (especially cholesterin and lecithin) also introduces important physical changes by altering the permeability of the cell and the aggregation of its colloids; on this rests the action of alcohol and the general anesthetics, of sapotoxin, and possibly of some toxins; a further action which is largely physical is the irritant effect produced by the introduction of foreign molecules into the cell. These must be conceived as acting as "molecular foreign bodies," disturbing the normal mechanism of the cell, even if they do not enter into any chemic reactions. It is often very difficult to draw a sharp line between these various physical action, and those which depend more strictly upon chemic changes, as there is a very intimate interrelation. The real insight into the **chemic actions** of pharmacologic agents is extremely difficult, because we are not sufficiently well acquainted with the chemic structure of protoplasm to conceive the nature of its reactions. From the fact that metabolism occurs, we deduce that chemic reactions occur, and these must be capable of modification by chemic reagents. From the complicated structure of the proteid molecules we conclude that it must be capable of a very great number of reactions, a conclusion which is confirmed by the large number of substances which are utilized by the cell. We find an expression of these chemic changes in the final excretory products of the cell; but we are very ignorant of the reaction by which these final changes are produced. When we find, therefore, that a chemic substance possesses actions for which there is no adequate physical explanation, we presume that it enters into chemic reactions with the protoplasm. In the simplest cases the actions occur on dead tissues, and resemble those produced on substances of known composition; this is the case with acids, alkalies, metals, etc. In other instances, analogous actions are produced on ferments; but in many cases, particularly with alkaloids, glucosids, and toxins, the action is confined to living cells, and for these we can generally furnish no explanation. The fact that these poisons are altered in the body, and that their effects increase with their dose, renders it very probable, however, that their action is also chemic. In the case of toxins this is confirmed by their chemic neutralization by antitoxins. The chemic combination is often very loose and unstable, as shown by the rapid recovery of small aquatic animals when they are removed from the poison to pure water. A strong evidence in favor of a chemic action is the:

Dependance of the Pharmacologic Action on the Chemic Constitution.— As a general rule, drugs having a similar constitution, possess similar actions; and definite changes in the molecule — as in homologous series, or the introduction of new groups — produce definite modifications in the pharmacologic effects.

This dependence of the action on the chemic structure has been established in a sufficient number of cases to give it the dignity of a general law. As with most biologic laws, however, there are numerous apparent exceptions to the general rule.

These apparent exceptions may very often be attributed to our ignorance of the true chemic structure of the poisons and of the protoplasm, for as our knowledge of chemistry increases, these exceptions tend to disappear. It must be remembered, for instance, that the action is not so much determined by the elementary composition of the substance, but rather by the manner in which the elements are combined. Isomeric compounds have often very different actions. Apparent exceptions result also from the different penetrability of cells to substances which, could they be introduced into the cell, would cause very similar effects.

The molecule of a poison often contains a number of groups of atoms, which have different actions. The recognition of which of these groups is the bearer of a given action is often of very great practical importance, for it enables the chemist to modify the molecule so as to give it the maximum of the desired therapeutic action, and at the same time to remove undesirable side-actions. This has led to the introduction of a number of synthetic remedies which are superior to natural drugs. Illustrations of these will be found in the groups of hydrocarbon narcotics, antipyretics, antiseptics, etc.

The Functional Manifestations of Pharmacologic Action.— Protoplasm has, broadly speaking, essentially the same structure, chemistry and functions, wherever it may be found. Considerable differences exist, for instance between a nerve cell and a gland cell; but these differences are mainly quantitative, and due to the specialization of the cell. Since protoplasm is essentially identical in all cells, the action of pharmacologic agents must also be essentially the same in all situations; but just as quantitative differences exist in the cell, so does the pharmacologic action show quantitative differences and selective properties. Of these we shall have more to say presently.

Pharmacologic agents can in no case create new functions in a cell or tissue; they can only modify existing functions, or at most make evident functions which have previously been latent. As a general rule, the most conspicuous changes occur in the most conspicuous function of the cell — partly because these are the most readily appreciated, but partly also because specialized functions are the most complex and hence the most sensitive. The functions of a cell may be increased or diminished, resulting in *stimulation* or *depression.* Since there are also structures the stimulation of which would lead to an inhibition of other structures, an actual increase of function is sometimes distinguished as an *excitation.*[1] A very violent stimulation passes usually into injury; such injurious stimulation is called *irritation.* Moderate, but prolonged, stimulation also passes into depression, either by the disappearance of food substances (*exhaustion*), or by actual injury to the structure (*fatigue*). If the depression is so great that the given function has disappeared, the condition is called *paralysis;* if all the functions are abolished, there is *death.*

The greater number of pharmacologic agents produce at first a stimulation, which is followed in larger doses by a depression. In this respect the differences between the different poisons are again mainly quantitative.

The so-called "stimulants" produce a very strong and prolonged stimulation, the depression being produced only by relatively large doses. The "depressants," on the other hand, cause only a slight stimulation, which passes readily into depression. Indeed, with a few depressants, no stimulation whatever can be made out. It is very rare that a depression precedes a stimulation; when this occurs, the action is presumably on different structures.

Selective Action.— It has been stated that the action of practically all drugs consists of a stimulation followed by a depression; and that these actions are exerted on every structure and on every function. It may be concluded from this that there must be a very great similarity in the effects of all drugs, and this is true if the actions are thoroughly analyzed. The differences which exist are in details rather than in principle; but they are none the less important. Indeed, these individual peculiarities are of immensely greater importance in the practice of medicine than the underlying similarity. The differences are attributable to the drug, to the cell, or to the interaction of different functions. They may involve a number of mechanisms:

(a) *Selective Absorption.*— A drug may act upon a cell without actually penetrating into it; for instance, by exciting the nerves supplying the cell, or more directly, by withdrawing water from the protoplasm; but as a general rule, the poison must be absorbed into the cell, before it can produce any action. In order that this absorption may take place, the drug must be either volatile, or it must be soluble in the cell contents, and particularly in the cell envelope. The solubility of a substance in protoplasm is not necessarily the same as in water. Indeed, it varies for each kind of cell, and consequently the penetrability of different cells for a given substance may vary greatly. Whilst the renal cells, for instance, are very permeable for sulphates, the intestinal cells are as good as impermeable. It is in virtue of this peculiarity that cells are capable of preserving their own composition, notwithstanding considerable changes in the fluids in which then are bathed. This fact also explains why a given substance acts much more strongly upon one cell than upon another.

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[1] For instance stimulation of the vagus would lead to an *excitation* of this nerve, and to a stimulation, but *inhibition* of the heart.

(b) *Effect of Concentration.*—The amount of a drug absorbed into a cell varies generally with the concentration of the drug in the surrounding fluid. This concentration is greatest at the place where the poison enters and leaves the body, *i. e.*, in the alimentary canal, liver, and kidneys. The influence of concentration is most readily seen with locally acting drugs. It appears, however, that with many poisons the effect is not strictly proportional to the concentration; for instance, increasing doses may produce very little effect up to a given point; when this is exceeded, very severe actions follow. This is due to the other factors entering into selective action, such as disintoxication, habituation, exhaustion, fatigue, etc.

(c) The poison may *act only on certain constituents*, which are present in different amounts in the various tissues. *F. i.*, ether, which acts by dissolving fatty substances, has therefore the greatest action on nerve tissue, in which fat is most abundant.

(d) The poison *may only unite with certain side chains* of the protoplasmic molecule, which are not present in every cell. This explains the selective action of toxins. The production of specific precipitins and cytotoxins is a strong proof of the individual chemic peculiarity of each class of cells.

(e) Certain cells possess the *power of rendering the poison harmless*, either by producing antitoxins, or by altering the chemical nature of the poison (as by oxidation or reduction), or by rapidly excreting the poison, or possibly by producing substances with an antagonistic action. This process of *disintoxication* is of very great practical importance. It makes it necessary to administer the drugs continuously, in order to maintain their effect; it often requires the use of continuously increasing doses as the power of disintoxication becomes more developed; and were it not for the power of the body to destroy or remove poisons, and thereby to recover from their action, all therapeutic use of drugs would be impossible.

(f) Certain cells appear to possess the power of *storing the poison*, *i. e.*, of absorbing it more readily than it is excreted. This explains the selective action of certain metals. (Intra vitam methylen blue staining is a conspicuous example of this selective storage; but many others could be given.)

(g) Some drugs are themselves innocuous, but give rise to *toxic decomposition products*. They will act selectively on those tissues where the conditions for the decomposition are favorable. *F. i.*, iodids are decomposed in the presence of acids with the liberation of the irritant iodin.

(h) The cause of selective action lies often in the cells themselves, *the more delicate functions being damaged more readily*. Hence a poison which acts indifferently on all tissues produces always the most conspicuous effect on the central nervous system.

(i) Certain cells also accommodate themselves more readily to altered conditions.

Pharmacologic Classification of Drugs.—The selective action of drugs permits a system of classification: Poisons which alter all tissues, and which therefore produce effects at the place where they are applied, are termed "*locally-acting*" drugs. They may produce similar chemic changes in dead tissues. These usually cause inflammation when applied to living tissues, and are then called *irritants* (including simple irritants, corrosives, and astringents). Others lessen inflammation mechanically (emollients and demulcents). Others act chemically on all living structures, without changing dead tissues; these are termed "*protoplasmic poisons.*"

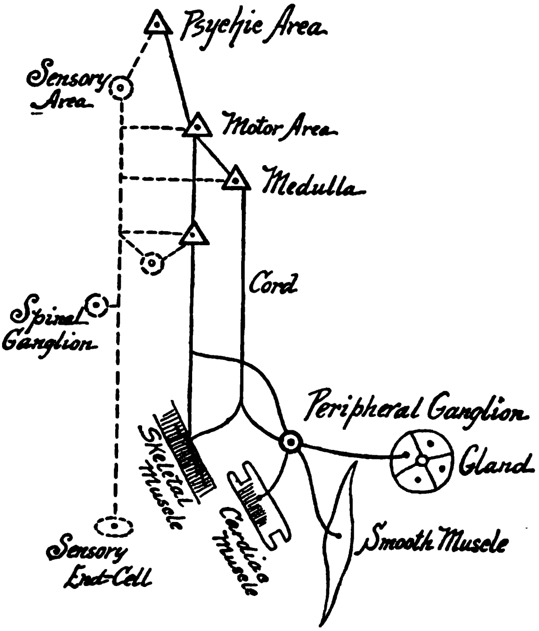

Fig. 44.—Diagram to illustrate possible points of attack of muscle-nerve poisons. The broken line indicates the afferent mechanism; the solid line, the efferent mechanism.

Poisons which act selectively on a few structures are called "**Muscle-Nerve Poisons.**" They may affect end-organs (sensory endings, gland cells, or striped, smooth or cardiac muscle); or the nerve-endings; or ganglia; or any part of the central nervous system. (Nerve-fibres are so resistant that they are only affected when the poison is applied to them directly.)

Variations in Symptoms.— The selective action of drugs is rarely absolute; even strychnin, a highly selective poison, acts as a general protoplasmic poison when it is directly applied in sufficient concentration. However, some one action often predominates so greatly over the others, that it may be considered as characteristic for the drug. Even in this case, the poison as a rule acts selectively on several structures. This accounts for the great variability which is often seen in the action of the same drug under different conditions. Thus, atropin stimulates the vagus center, but paralyzes the endings: it may therefore cause either a quickening or a slowing of the pulse. Again, through the opposed action of small and large doses, strychnin, *e. g.*, may cause either a stimulation or a paralysis of the vasomotor center. Another frequent cause of variable actions lies in the indirect actions of a drug. A drug which causes convulsions will thereby tend to stimulate the vasomotor center, although its direct action on this center may be depressant.

Drugs which act upon the vasomotor center are particularly apt to give rise to indirect effects, *f. i.*, on the central nervous system, which are apt to be mistaken for direct action. This is well illustrated by the systemic action of metals. These variable actions and interactions make the effects of many poisons appear very complicated, although they prove quite simple on analysis. This analysis is very important for a proper understanding of the action, but it is still more important to remember the complex effects which result, for it is with these that the practicing physician has to deal. Very often the pharmacologic action in this sense is not the therapeutic action. A very important pharmacologic action of morphin, for instance, is a stimulation of the spinal cord; but no one would think of employing the drug therapeutically for this purpose, since this action is entirely overshadowed by its other effects. For this reason it would not be a good plan to classify the drugs strictly according to their pharmacologic actions. On the other hand, a therapeutic classification, although useful in some respects, is not favorable to a study of the underlying actions of the drugs, and tends to empiricism. The best principle of classification yet devised is that of Buchheim,[1] according to which drugs are grouped according to their principal pharmacologic characters, taking account of all the important actions, as well as of the chemic properties,[2] and in many cases also of the therapeutic uses of the drugs. In this classification the actions of one group shade off into those of the next, the system resembling somewhat that of the natural system of orders used in botany or zoology. This is the general plan which, with minor modifications of detail, has been adopted in this volume, the pharmacologic classification being supplemented by therapeutic summaries. With this arrangement, it makes very little difference with which group the study of pharmacology is begun. If the student is well grounded in physiology and pathology, it is well to begin at once with the muscle-nerve poisons; otherwise it will be found best to begin with the locally acting drugs (Chapter XXVIII).

Definitions of Pharmacologic Terms.— Some rather loosely used pharmacologic terms may be defined in this place, in the sense in which they are generally employed in this volume:

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[1] Buchheim may be considered the founder of modern pharmacology, by the establishment of the first pharmacologic laboratory, at Dorpat in 1856.

[2] Drugs of very different chemic character often appear to have identical actions. Thus the action of strychnin resembles that of tetanus toxin, arsenic that of cholera, barium that of digitalis. In some cases the action may be supposed to be really identical, but in others the resemblance is merely superficial.

Local actions: produced at the place where the drug is applied; *Remote actions:* occurring in distant parts of the body (may be either systemic or indirect); *Systemic effects* (sometimes called general action): produced after the absorption of the drug into the circulation; *Direct effects* (sometimes called primary): produced by the direct action of the drug on the tissue concerned; *Indirect effects* (sometimes called secondary), are not produced by the action of the drug on the tissue concerned, but by the intervention of some other structures on which the drug acts (*e. g.,* asphyxial convulsions are an indirect effect of asphyxiant poisons); *Reflex effects* are indirect actions arising from local irritation; *Immediate effects* (also sometimes called primary) are the effects resulting at once; *Late effects* are those occurring later; if they are preceded by other (immediate) actions, they are properly called *secondary actions. Side actions* are actions which are not desired in the therapeutic use of the drug.

Method of Pharmacologic Investigation.— The effects of drugs on patients, or in cases of poisoning, are by far too complex to furnish any real insight into the actions which are involved. To attain the object of pharmacology — the explanation of the action of drugs — it is indispensable to simplify the conditions as much as possible, and to make the functions, which are to be studied, accessible to measurement, and if feasible, to graphic representation. The methods of experimental physiology are employed for this purpose.

The Study of Isolated Structures.— To eliminate the complications which arise from a simultaneous action on several structures or from indirect actions, the tissues to be studied are generally isolated. This isolation may be accomplished by employing unicellular organisms if the action on undifferentiated protoplasm is to be investigated; or by excising the tissue (as muscle, etc.) from the body; or by applying the drug to the exposed tissue (*e. g.,* to a sympathetic ganglion); or by severing the connection with other tissues which might be affected (as by section of a nerve); or by paralyzing these structures by appropriate poisons; or by restricting the action of a drug to a given part, by cutting off the circulation. In some cases it suffices to confine the observation to the structure to be studied.

One or the other method of isolation may be employed, according to circumstances; that giving reliable results with *the least difficulty of technic* being naturally preferred. Complete isolation is in many cases superfluous. If the question is, for instance, whether an observed **stimulation** is on a central or on a peripheral structure, it suffices to divide the nerve: on an efferent chain, this will abolish the effects of a central stimulation, whilst those of a peripheral stimulation will persist. With an afferent chain the conditions would be reversed. By making sections at various levels of the chain, the location of the action may be accurately determined. When the structures to be investigated are inaccessible to the scalpel, one may substitute drugs which are known to paralyze these structures selectively. (Chloral for vasomotor center; quinin for muscle; curare for the endings in striped muscle; nicotin for ganglia; atropin for endings of the vagi or sympathetic, etc.) The **site of a paralysis** is similarly located by successive stimulation. The stimulation is accomplished by electricity or by appropriate drugs (*e. g.*, physostigmin for muscle and for sympathetic endings; small doses of nicotin for ganglia; muscarin for vagus endings; pilocarpin for glands, etc.).

A few examples will make this general method clear:

1. *Strychnin.*[1]— It is noted that strychnin produces a tetanus. This implies a motor stimulation somewhere. The sciatic nerve is cut; it is found that the convulsions disappear in the leg but persist in the rest of the body. The action must therefore be central. The cerebrum and medulla are successively excised; the convulsions persist, and must, by exclusion, be located in the cord. This is confirmed by destroying the cord, which causes the complete disappearance of the tetanus.

2. *Curare.*[2]— This produces a complete muscular paralysis. Stimulation of the sciatic elicits no response. The paralysis must therefore be peripheral. Direct stimulation of the muscle is effective. This excludes all the possible structures except the nerve trunk and endings. The nerve of another preparation is laid into the curare solution, and after a time, is stimulated; a contraction results, so that the nerve trunk is not paralyzed. The action must therefore be on the endings.

3. If a peripheral structure is stimulated or paralyzed, it is impossible to decide by this method whether there is not also a central action, for the peripheral effects would obscure the central. A stimulation of the cord, for instance, could cause no effect if the drug had paralyzed the motor endings. In these instances, it is necessary to confine the action of the drugs to the centers, which requires a more complicated technic.

The Study of the Effects of Drugs on Intact Normal Animals.— A complete conception of the actions of a drug can only be obtained by supplementing the study of its effects on isolated structures, by careful observation and analysis of the symptoms which it produces in intact mammals. The effects on metabolism, and the histologic lesions, etc., can only be studied in this manner. Indeed, these experiments are often undertaken before the more difficult investigations on isolated structures; for they furnish valuable hints of the direction which the latter should take. When circumstances permit, it is advisable to proceed from the lower to the higher classes of animals, and finally to man. Opportunities for observing ***the effects of drugs on man*** are frequent in cases of poisoning, and should not be neglected; but intentional experiments with drugs on man are to be undertaken only with the greatest caution, with doses which do not exceed the therapeutic maxima; and, as a rule, only after the effects have been thoroughly studied on animals.

The Effect of Drugs in Disease.— The action of drugs is not always the same in disease as in health. The differences are, however, as a rule quantitative rather than qualitative. Since the drugs are in practice employed most extensively in disease, their action in these conditions is of the greatest importance. As a general rule, it is possible to explain, and even to predict, the action of drugs in disease from their action on normal tissues. However, the actual test must always be made. Animal experiments are of but limited value in this connection, and we are forced to rely mainly on observations on patients. To make these of any value it is in the first place necessary that the observations be made very accurately and that all psychic factors be excluded; it is further necessary that the existing pathological condition be correctly known. These requirements are unfortunately not fulfilled in many cases, which accounts in part for the differences which are occasionally noted between the clinical and the experimental data. These exceptions will be discussed in the text.

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[1] Exercise 38.

[2] Exercise 42.

In the case of all the older drugs, clinical tests have been made so abundantly that further observations would seem superfluous. This is by no means the case. Accurate observations in the light of our advancing knowledge, and employing the improved methods of diagnosis and observation, are always needed.

It is also highly desirable that every physician should obtain his knowledge of the therapeutic action of drugs at first hand. He should utilize every case under his care for this purpose, and conduct his treatment as if it were a critical experiment, the interests of the patient being, of course, paramount. The conclusions will be greatly simplified if but one drug is used at a time.

Chemic Investigations.— Since the action of drugs depends so largely upon their *chemic constitution,* the latter is a legitimate subject of pharmacologic inquiry. The study of the *fate of the drug* in the body, of the *mechanism of its absorption, excretion, and storage,* is also indispensable. These involve the method of quantitative chemic analysis.

The Practical Value of Pharmacology.— The utilitarian aim of pharmacology is to supply the science of medicine with a rational and scientific basis for the practice of therapeutics and for the study of toxicology. It was shown in the preceding section that these objects can only be attained by experimentation on lower animals. This brings up the fundamental question: *To what extent can results observed on animals be transferred to man?* The prejudices in regard to this question — which concerns all fields of medical research — have fortunately disappeared almost completely. It is now conceded that *a similar physiology implies a similar pathology and pharmacology.* In the great majority of cases, similar structures are affected in the same way by a given drug, no matter in what animal they are studied.

Racial Peculiarities.[1]— Where differences exist, these can usually be explained by *differences in the physiologic functions.* For instance, the cerebral actions are usually the more pronounced, the more highly the central nervous system is developed; whereas spinal actions predominate in the lower vertebrates. Rodents are incapable of vomiting and are therefore not affected by emetics. Atropin quickens the heart of the dog, but not that of the rabbit, because it acts by paralyzing the vagus, which is not tonically active in the rabbit.

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[1] Exercise 28.

There are still a number of differences which *can not yet be explained on a physiologic basis,* as *f. i.* the tolerance of rabbits, etc., to the toxic effect of atropin. These must be referred to our ignorance of the physiologic differences which are involved. The differences in animals, physiologic and unexplained, are now generally recognized so that suitable species can be chosen for experimentation. They can furthermore be eliminated by using the drug on several species: *If a given poison affects all species alike, it may be concluded that its action on man is also the same.* If it produces different effects, but if these can be explained by differences in physiology, the effects on man will be similar to those produced on the species the physiology of which resembles most closely that of man.

It will be seen that great care must be used in applying the results of experimental pharmacology to man. The neglect of this precaution, the drawing of far-reaching conclusions from a few limited experiments, threw discredit on pharmacology in its earlier days, and is still seen all too frequently. Pharmacology cannot be held responsible for this misapplication of its data by half-trained enthusiasts. Its scope is really limited to its own results and not to their application, although it may legitimately suggest the latter. It should not be made to replace the science of therapeutics, but should only aim to place well studied tools in the hands of the latter. If this limitation is realized; if the therapeutist will carefully study the results of pharmacology and will utilize and interpret them in the light of bedside experience, then pharmacology will be of very great value to medicine.

One very important service is rendered by pharmacology through the examination of new remedies. The development of synthetic chemistry especially has resulted in the discovery of a very large number of new substances of some therapeutic value. The number is indeed so large, that all could not be given a thorough trial on patients. Most of these substances possess some value, but many differ from each other by very insignificant details. In this case, pharmacology can select the most promising drugs of a type, and by their thorough study, indicate those which are worthy of trial by the clinician.

CONDITIONS AFFECTING THE ACTION OF DRUGS.

The effects of a given drug or poison are not always uniform, but vary with conditions; such as the dose; the absorption and elimination; the method and time of administration; the simultaneous presence of other substances; the age, sex and race of the patient; the existence of disease, etc., etc. A knowledge of these variations is very important.

Dosage.—Drugs are administered to produce a desired effect, and the dose must be sufficient for this purpose, and neither too small, nor too large. Since the effect is influenced by numerous conditions, it is impossible to state the exact doses for any drug; experience is the only safe guide. However, the doses vary under ordinary conditions only within rather narrow limits, and lie near the "*average* *doses*" given in this book. The U. S. P. also states the average doses. The "*maximum dose*" signifies the largest dose which can be safely used in ordinary cases; the "*minimum dose*" is the smallest dose which produces therapeutic effects; a "*toxic dose*" is one which produces dangerous effects; the "*just fatal dose*" is that which is just sufficient to cause death; the "*physiologic dose*" (a rather indefinite term), is used in physiologic experiments on animals.

Daily Dose.— The single doses are usually calculated on the assumption that sufficient time is allowed to elapse between the doses, for the greater part of the drug to be excreted. This constitutes a *periodic medication*. The exact time varies of course with the nature of the drug, but in most cases the drug is administered three or four times a day; so that the *daily dose* is about three or four times the single dose. If a *continuous action* is desired, correspondingly smaller doses are given at shorter intervals.

The doses ordinarily stated in text-books apply only to adults of average size, and to oral administration.

Effect of Weight.— Other things being equal, the effect of a given dose is inversely proportional to the weight of the individual (exclusive of the adipose tissue). It is rarely necessary to make allowance for the weight in adults (20 to 60 years), but it may be used for calculating the doses for children.

Calculation of Doses for Children.— In most cases, the adult dose is reduced in simple proportion to the weight of the child — either by direct calculation, or by the use of empiric rules based on averages, as described below. The dosage so obtained is generally sufficiently exact. It is inadmissible only with extremely young children; and with drugs the action of which is influenced specifically by age.

Clark's Rule.— Multiply the adult dose with the weight of the child (in pounds), and divide by 150 (the weight of the average adult). This rule gives the most exact results.

Young's Rule.— Multiply the adult dose with the age of the child (in years), and divide by the age plus 12.

Cowling's Rule.—Multiply the adult dose with the age of the child at the next birthday, and divide by 24.

(For example, by Young's rule, the dose for a child of three years would be $^3/_{15} = ^1/_5$ the adult; by Cowling's rule, it would be $^4/_{24} = ^1/_6$.)

The dose for aged people is generally taken as somewhat less than that for adults. Above 60 years, the latter is reduced to ⅘ or ⅔; and in extreme senility, to ½.

Specific Influence of Age on Drug-Action.— These (*i. e.*, apart from the difference due to weight) are only known definitely for a few drugs, although young individuals are quite generally more sensitive to drugs than adults. Children are especially susceptible to morphin and nicotin, and comparatively tolerant to strychnin. Old age is also less resistant to drugs; purgatives and emetics are especially debilitating. The frequent existence of atheroma makes it dangerous to use drugs which raise the blood pressure, directly or indirectly.

Influence of Sex.— Women usually require somewhat smaller doses than men (½ to ⅘). The greater susceptibility is in large part due to the lesser weight, but in part also to the anatomic and functional peculiarities. The influences of sex are of course most pronounced with drugs which act on the generative organs. **Pregnancy** also modifies the action of drugs, and contraindicates the use of irritant cathartics (because of the danger of inducing abortion) and of irritant diuretics (on account of the tendency to nephritis), etc.

The **temperature** has a marked effect in cold-blooded animals; veratrin, nicotin, strychnin, tetanus toxin, chloral, and alcohol, for instance are rendered more active, morphin and curare, less active, by raising the temperature. An indication of this influence in man is seen in the modification of the action of antipyretics by fever. (In mammals, cooling generally increases the fatal effect by adding its direct depressant action.)

Pathologic conditions must also be taken into account. These may lessen absorption (diarrhea) or increase it (corrosion); they may hasten the destruction of the poison (alcohol produces less intoxication in fever); or they may alter the effects entirely (the antipyretics reduce the temperature in hyperpyrexia, but do not effect it when it is normal; mercury produces peculiar effects in syphilis; digitalis is an efficient diuretic in cardiac disease, but not in health; it affects the normal cardiac muscle, but has little action on a fatty heart, etc.). These modifications are readily explained by the functional or anatomic changes of disease.

Synergism and Antagonism.— The effect of drugs is similarly influenced by unusual conditions induced by the *simultaneous administration or presence of other drugs.* The effect will be greater, and the dose should be smaller, if another similarly acting drug is being given. In some instances the simultaneous effect of several drugs is greater, or more desirable, than could be secured by the action of one drug alone, even were it given in increased doses. This phenomenon, which is called "*synergistic action,*" has not been sufficiently investigated experimentally, although it is of frequent occurrence, and of great importance. In some cases it is due to the summation of useful actions, whilst undesirable side actions are neutralized. The drugs must be present in certain proportions, else the effect may pass into antagonism.

In other cases, new actions are developed by the reaction of the drugs on each other, with the production of new compounds. For instance, the presence of acids renders the basic salts of bismuth soluble and toxic; it liberates iodin from iodids; the iodids also decompose calomel and render it irritant.

On the other hand, drugs may oppose each other, *i. e.*, have an "*antagonistic action.*"[1] This constitutes "*therapeutic incompatibility.*" The antagonism may be due to opposite actions, to chemic neutralizations or to interference with absorption, or to increased excretion (for instance, the chlorids increase the elimination of iodids and bromids, and thereby lessen the action).

The time of administration also influences the action of drugs. Hypnotics and Cathartics, for instance, are most effective when their action coincides with the natural time of sleep and defecation, and if the external conditions are favorable. Stomachics are best given shortly before meals. Drugs which are to be absorbed rapidly are given on an empty stomach, whereas irritants are administered just after meals, when the stomach is protected by food; etc.

The preparation of the drug is also important. Extraneous matter delays absorption, so that the isolated active constituents (alkaloids, etc.) are preferred if a quick systemic action is desired, whilst the galenic preparations (extracts, tinctures, pills, etc.) are used for local effect. In case a crude drug contains several active ingredients, the employment of the isolated constituents will give more certain results.

Absorption.[2]— The time required for the absorption into the body and into the cells varies from a few seconds (*e. g.*, hydrocyanic acid), to several weeks (*e. g.*, lead). The rapidity of absorption depends upon the nature of the drug, the place of administration, and a number of accessory factors. It is generally proportional to its *solubility in protoplasm or to its volatility.* It must be remembered that the solubility in water is not always an index of the solubility in proteid containing fluids, and particularly in protoplasm. The solubility may also be modified in the alimentary canal. The rapidity of absorption is also proportional to the *rapidity of the circulation* in the absorbing surface; it may also be hastened (especially from subcutaneous injection) by increasing the lymph-flow through *moderate distention* and through *massage*. It is also hastened by increasing the absorbing surface (*e. g.*, by making *multiple hypodermic injections*). It is further hastened (especially with hypodermic injections) by increasing the *concentration* of the drug. *Decrease of the circulation* (deficient heart action, venous stasis, vasoconstriction) delays the rapidity of absorption. In the alimentary canal, *injury to the absorbing cell may* either facilitate or hinder absorption; *astringents* tend to have the latter effect, *corrosives and simple irritants* the former. The presence of *oil, gums, or extractives* lessens absorption by hindering the access of the drug to the absorbing surface.[1] The presence of food in the alimentary canal has a similar action. On the intact skin, however, absorbable oils facilitate the absorption of other substances dissolved in them; alcohol has a similar favorable effect in the stomach.

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[1] Exercise 29.

[2] Exercise 24.

The channel by which drugs are absorbed into the body depends naturally on the *place of administration.* Absorption of drugs may occur from the alimentary canal or from other mucous surfaces; from subcutaneous tissue or serous cavities; from the alveoli of the lungs (gases and volatile substances); a limited number of substances may also be absorbed from the intact skin. The influence of the place of administration will be discussed later.

It must not be forgotten that a drug, after it has been absorbed into the circulation, needs still to penetrate into the cells. This intracellular absorption depends upon the nature of the poison (selective absorption), and to some degree on its concentration. As a rule, it is a very rapid process: Masoin (1903) found the time which elapses before just toxic doses disappear practically completely from the blood, after intravenous injection, to be for Arsenic, $^9/_{10}$ to 30 seconds; Tetanin, 20 seconds; Cyanids, 2 to 6 minutes; Diphtheria toxin, 4 minutes; Antitoxin, several hours.

Excretion.[2]—This occurs through the urine, feces, expired air, sweat, and through all the secretions. It is proportional to the circulation and to the functional activity of the excretory organs, and may be increased by the factors which stimulate these. The excretion of certain drugs appears to be limited by their existing in the body in the form of combinations. The elimination of these is favored by substances which displace them from the compounds. This is probably the explanation of the increased excretion of iodids on the administration of chlorids, and possibly of the favorable effect of iodids in chronic poisoning by metals.

Fate of the Poison.—The majority of poisons are more or less altered in the body, and rendered less harmful. This is effected by the oxidation, reduction, or decomposition of the poison, or by the storage of the poison in certain organs, or by its combination with other substances which render it harmless. A few examples of the *mechanisms of disintoxication* may prove interesting:

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[1] Exercise 25.

[2] Exercise 26.

Strychnin and many other poisons are partly oxidized in the body, and the toxic effect is therefore reduced if the poisoned animal is placed in an atmosphere of oxygen. Caffein is said to be more toxic to animals deprived of thyroids, which might be explained by the lesser oxidation following the removal of these glands. Reid Hunt (1905) has shown that feeding with thyroid markedly diminished the toxicity of acetonitril. The action of some poisons, particularly the toxins, is destroyed by the chemic action of the gastric juice. Morphin is also largely destroyed somewhere within the body, especially in individuals accustomed to its use. The benzol-ring is very resistant, most of the changes occurring in the side-chains. The liver is very active in disintoxication, partly by destroying, but particularly by storing poisons, so that the same dose is much less effective (perhaps one-half) when given by the mesenteric, than by the jugular vein. This has been demonstrated[1] for curare, strychnin, morphin, cocain, veratrin, quinin, atropin, and the metals. (Mercury is stored mainly as a rather loose globulin compound, arsenic as a stable nuclein combination, De Vamossy, 1905.) Splenectomy increases the toxic action of a number of alkaloids, but not of all. The spleen also participates in the deposition of metals; the bones retain fluorin and barium; the central nervous system strychnin, lead, and arsenic; etc. The phagocytes also accumulate poisons, dissolved as well as solids. Carbolic acid and other aromatic compounds are rendered less toxic by combining with sulphates; many metals by the proteids; toxins by antitoxins; acids by alkalies; camphor, chloral, and ethereal oils by glycuronic acid; cyanids by sulphur; benzoic and salicylic acid by glycocoll; etc. The extent of the disintoxication will depend upon the activity of the metabolic process which are concerned, or on the amount of neutralizing substance present in the body.

Idiosyncrasy.— This term (from *ἴδιος*, one's own, and *σύνκρασις*, a blending) is applied to peculiar, exceptional reactions to the effects of drugs. The differences are generally quantitative, and may concern the main action, or the side actions. They may be inherent in the remedy, or may be due to extraneous causes, or they may be referred to the constitution of the patient. In the latter case, they may be due to anatomic or to functional peculiarities. They may be congenital or acquired, temporary or permanent. (Many apparent instances of idiosyncrasy are doubtless due to differences in the strength or constituents of drugs.)

Idiosyncrasy in Animals.—Racial idiosyncrasy was already discussed on page 125; but in animals, as well as in man, peculiarities exist in different individuals of the same species. *Qualitative differences* are seen particularly in the action of Cannabis on dogs (Exercise 24).

Instances of *quantitative differences* are very numerous:

In a large series of experiments with toxic doses of drugs on animals the author has found that there is a fair degree of uniformity in the proportion of animals which died with a given dose. Thus, certain limits can be found inside of which, out of five animals three will always die. These limits vary from 0.5% (strychnin) to 25% (ergot), but are usually comprised within from 5% to 10%.

On the other hand, the susceptibility of any one animal is subject to greater possible variations; *e. g.,* with a given preparation of digitalis, 0.6 mg. per gram will always kill three guinea-pigs out of five.

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[1] Experiments on dogs with Erk's fistula render it rather doubtful whether the liver disintoxicates alkaloids much more actively than other tissues. (Rothberger and Winterberg, 1905.)

But in a large series of experiments, a number of animals will be found which will die of doses as small as 0.4 mg., while others will die only when 0.9 mg. is reached. Whether these comparatively immune animals always enjoy this immunity, or whether the condition is only temporary, as well as the influence of age, sex, etc., has not been determined.

These individual differences are still more striking if, instead of observing the toxic doses,—*i. e.*, the sum total of the effects,—we direct our attention upon some one particular action, *e. g.*, the amount of slowing of the heart or the variation of blood pressure. The differences in this respect are so great qualitatively that it is undoubtedly unsafe to draw conclusions from a single experiment, and it is absolutely impossible in these cases to establish any quantitative standard.

Increased Susceptibility.— This may be due to very rapid absorption, or slow elimination; to the presence or synergistic agents in the body; or to increased functional susceptibility.

Cumulative Action.— By this is meant an acquired susceptibility by which a given dose will produce greater effects than it did originally. This may be brought about in several ways: by greater capacity for absorption than excretion (lead); by inconstant absorption, where successive doses of the drug may lie unabsorbed in the alimentary canal, to be finally taken into the system *in toto* when the conditions are favorable to absorption. This is frequently the cause of the cumulative action of digitalis, and it explains the fact that the greatest individual variability to toxic doses exists precisely for those drugs which are absorbed with the greatest difficulty.

Cumulative action may also arise through *summation of effects*. The effect of the preceding dose may not have disappeared when the succeeding dose is given. The system appears also to be subject to what might be called an "education" to the effects of the drug. This is seen particularly in drugs acting upon the central nervous system. It is found, *e. g.*, that the susceptibility to strychnin increases with its administration, and it would seem that this is caused by the central nervous system becoming educated to the stimulating actions and responding to them more readily.

Another cause of cumulative action is the lowering of the resisting power produced by the preceding doses, or by using up the products required for the neutralization of the poison.

Tolerance.— This may be due to non-absorption, to rapid elimination, to the neutralization or destruction of the poison, or to anatomic peculiarities. Many cases cannot be explained in this manner, and must be assumed to be functional (the "histogenetic" immunity of Behring). To this class belongs the tolerance of the hedgehog to many poisons; of the toad to digitalis; of the chicken to cantharidin, etc.

The tolerance is rarely absolute, so that it is scarcely correct to speak of "immunity."

Habituation.— Tolerance may be congenital, or it may be developed by the repeated administration of the poison. This habituation may be functional (alcohol, caffein, nicotin?); or it may be due to increased destruction of the poison (morphin); or to the production of antibodies (toxins).

It is an interesting fact that functional habituation, when acquired for a particular drug, may hold also for other drugs having a similar action. A habitual drunkard, *e. g.*, is resistant to the general anesthetics. Whether this extended immunity also holds true of other allied drugs, such as morphin and cannabis indica, has not been determined.

Impurities in Drugs.— Qualitative abnormalities in the effects of drugs are usually due to the *exaggeration of a side-action;* but in some cases they may be referred to the presence of impurities. It is rather doubtful, however, whether these impurities have the importance which is often assigned to them. Whilst it is undoubtedly desirable that drugs should be as pure as it is practical to make them, minimal amounts of foreign substances cannot be said to be very objectionable, unless they are particularly poisonous. The pharmacopœias have taken a wise stand in this matter by permitting the presence of small amounts of such impurities which it would be very difficult and costly to remove.

Methods of Administering Drugs.— The channel by which a drug is introduced into the body, or the place to which it is applied, must vary with the object to be secured — whether the action is to be local or systemic; the desired rapidity of absorption; the necessity of avoiding irritation of certain organs, etc.

Local Administration.— Drugs may be used locally either to protect a surface, or for reflex effect, or as antiseptics, or as stimulants. They may be applied to the skin in various vehicles: If it is desired to secure the absorption of the remedy or its deep penetration, vegetable or animal oil must be used, preferably adeps lanæ hydrosus (lanolin). Oleic acid presents the advantage that it holds certain substances in true solution (metallic oxids and alkaloids). Where the local effect alone is required, the mineral fats (petrolatum or vaselin) may be employed. The remedy may also be placed in aqueous solutions (washes), especially if intended for an antiseptic; or it can be used in powder form. Caustics may be used either as solids or liquids. Counter-irritants are used as liniments, *i. e.*, dissolved in oil, turpentine, or alcohol.

Local medication may be used also on other surfaces than the skin, if they are accessible; *e. g.*, mucous membranes. They are usually applied as aqueous solutions (injections, washes, and gargles).

Local application to the skin can be used for producing general effects, but it is only employed in those cases (mercury) where the stomach has to be avoided and subcutaneous administration is not possible. The principal objection to the administration of drugs by the surface of the skin consists in the uncertain absorption, an exact dosage being in consequence impossible.

Watery solutions are not absorbed from the skin, unless the drug is volatile or caustic. The reason for this non-absorption lies in the fact that the stratum corneum of the epidermis is absolutely non-permeable to solutions. Absorption must take place through the glandular structures of the skin, and these are filled with fatty matter, which prevents the penetration of watery solutions, but not, of course, of other fats.

It must be borne in mind that the application of solutions to open wounds or abraded surfaces is practically the same as subcutaneous injection, and absorption occurs in this case very readily.

Oral Administration.— This, the most ancient method, is still the standard one. Its advantage lies in its great convenience and in the absence of local irritation. Nevertheless, certain drugs do give rise to disturbances of digestion.

This can be avoided by giving them in such a form that they will not be dissolved in the stomach (pills), or by giving them at a time when the stomach is filled with food. Absorption is, of course, delayed in these cases.

The *relative rôle of the stomach and intestine* in absorption varies for different drugs and animals. Strychnin, *e. g.*, is absorbed from the stomach with dogs and cats, but not with rabbits and guinea pigs; whereas sodium salicylate and iodid give just the opposite result. Inoye and Kashiwado (1905) have shown that atropin and rhubarb are not absorbed from the dog's stomach, whilst salol is absorbed. The data as to man are insufficient.

Rectal Administration.— The stomach and small intestine may be avoided by giving the drugs per rectum, either in the form of enema or suppositories.

Enemata, when introduced for the absorption of the medicine, should be as small as possible, but not so strong as to produce local irritant effects. One or two ounces is usually the proper quantity. The dose per rectum is generally double that by the stomach. When enemata are employed for their mechanical effects, the amount must, of course, be much greater — one or two pints. These should be raised to the body-temperature.

The rectal dose may approach very closely to the subcutaneous, especially with very active poisons.

Subcutaneous or Hypodermic Administration.— This method, which was introduced by A. W. Wood in 1855, has the advantage of being quicker and more certain in its effects, and the dosage is more exact than can be secured by any other method. The principal objection to it lies in the fact that while it is not very painful with some medicines, it is very much so with any irritating substance. There is also a tendency to abscess formation. This is frequently due to deficient asepsis, but certain substances (protoplasmic poisons) produce abscess formation even with the most rigorous asepsis. The hypodermic dose is about one-half of the oral dose.

Hypodermic injections are usually made under the skin of the forearm. For very bulky injections, *e. g.*, for antitoxin or for saline solution, the loose areolar tissue of the subscapular or mammary region is chosen.

It may be recalled that the *rapidity of absorption* from hypodermic injections may be hastened by massage, by distributing the injection over several places, and by dissolving the drug in a *small* amount of fluid. The concentration in salts should not exceed that of the blood, or the injection will be painful. Normal saline solution is the least irritant solvent for alkaloids. Subcutaneous injection is naturally inadmissible if *local* effects in other parts of the body are desired (*e. g.*, for stomachics, cathartics, locally acting emetics, etc.).

Intramuscular injections are made by thrusting the needle through the skin deep into the substance of the gluteal muscles. The absorption is more rapid than with subcutaneous administration (Meltzer and Auer, 1904), and the irritation and tendency to abscess formation are less.

Intraperitoneal and intrapleural injections are used in experimental technic, and resemble subcutaneous injections, the drug being absorbed more rapidly. Intraperitoneal injections in man have been made by Schmidt and Meyer (1905), but are not recommended.

Injections into the trachea are very rapidly absorbed through the alveolar capillaries, and act more like intravenous injections. They also cause asphyxia, and are not used intentionally. Tracheal sprays are used for local effects.

Intraarachnoid injections are used if the drug is to act directly on the spinal cord. The technic is that of lumbar puncture, some cerebro-spinal fluid being withdrawn before the injection is made. The procedure is dangerous, since the poison may be conveyed directly to the medulla.

Intracerebral injections (*i. e.*, into the substance of the brain) have been used experimentally. The injections are at once conveyed to the ventricles and produce local and mechanical effects very different from the systemic action of the drug.

Intravenous Administration.— This is very often used in pharmacologic experiments. Clinically, it has been tried in recent years, but has not come into general use. While it is the quickest way of securing the action of the substance, the slight operation required is some objection. There is also considerable danger connected with it. Air may be introduced into the vein, and while the presence of a small bubble of air in the circulation of a man is not as dangerous as in that of a rabbit, it may lead to very serious results. Another factor which we have already mentioned is that the action of drugs injected intravenously may be quite different than when taken by other channels. They act upon the heart more directly and with less dilution. Many substances also have the property of clotting the blood, and unless the administration be very skilfully done, the result might be disastrous.

Inhalation.— This method is used only for gaseous medicines, such as anesthetics or oxygen.

When giving drugs by inhalation, it must be borne in mind that the effect does not depend upon the quantity given, but the concentration of the gas and the time during which it is administered.

Cataphoresis.— This process has been employed in dentistry to facilitate the penetration of cocain, but it has not as yet found very extensive adoption in medicine and surgery. It is a process by which the molecules are carried from the + to the — pole. The solution to be introduced must possess a higher conductivity than the liquid of the tissues.

HISTORICAL DEVELOPMENT OF THERAPEUTICS.

If we cast a glance at the history of therapeutics, we are met with some very singular facts. Some of these will serve to explain errors which have long adhered and which still adhere to the subject.

We may imagine one of our remotest ancestors brought face to face with disease. How mysterious must have seemed to him the phenomenon that to-day he is strong, active, and full of life, and to-morrow, without any cause apparent to him, he is weak, listless, and about to die! What strong hold it must have taken upon his untutored imagination! How earnestly he must have sought for means to remedy it! Here he happened at once upon two apparently very different methods: a spiritual and a material. On the one hand, overpowered by the mysteriousness of the process, he lost himself in superstition. He deemed the disease due to malevolent spirits which could be appeased by prayers and incantations. This formed the principal materia medica of prehistoric ages, as it does of the modern savage.

On the other hand, chance and the observation of animals revealed to him that certain material products were also efficient. As long as he limited himself to actual observation, the results were usually good. However, he soon began to search for more of these remedial agents. In this search we must remember the total ignorance which then existed regarding the nature of the action — both of the disease and remedy. In this darkness he was only too glad to be guided by any ray of light, without having the means to examine whether the light came from a beacon or was only an ignis fatuus. With the fantastic, half logical incongruity so characteristic of the untutored mind he assumed the most extraordinary relations.

It is interesting to observe a little closer the principles which guided the blind savage in his search for remedies. Having found that most active medicines had a bitter or disagreeable taste, he came to regard any such substance as beneficial. Thus arose a host of simples which are now stowed away to molder in the attic of science, and which might well be disregarded were it not that some zealot occasionally disturbs their well-earned repose and attempts to launch them as something new.

Nor did this love of the disgusting die out with the stone age. It was prolonged far into the middle ages. To it we can probably trace the employment of feces and urine, of smoked snake, and of others still worse.

At a later period of the middle ages it was tried to combine the spiritual and the material treatment. It was thought that the Deity alone could cure disease, but that He had given man material remedies, and in His wisdom He had put a seal upon them by which man might know them. Thus arose in due time what is called the doctrine of "signatures." According to this, the use of a remedy was suggested by a fanciful resemblance in shape or color to some organ; *e. g.*, the liverwort, the lungwort, bloodroot, etc. These are survivals of this custom. Even a name was sufficient. Silver was used in lunacy because it was dedicated to Luna.[1]

On the other hand, alchemists had arisen with their pertinacious search for the philosopher's stone, which was to convert all metals into gold, and cure all diseases. In this search they gave their nostra extensive trial on sick and well. Antimony is related to have been so named by its discoverer because of its fatal effects upon his fellow-monks.

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[1] It would appear that the native Chinese materia medica is largely based on the dotrine of signatures.

The school of spagirists was founded by Basilius Valentinus toward the end of the fourteenth century and reached its zenith of power with Paracelsus. They insisted upon the mystical virtues of Sb, As, and Ag, and chemicals in general, and stood opposed to the old Galenists, who used only organic drugs. Notwithstanding their mysticism, which flavors of quackery, we must thank them for the discovery of some of our most valuable medicines.

Thus, a mass of materials, rubbish and otherwise, was added to the various simples, etc. Having so well-stocked an armory, the physician of that day felt that he was not doing his duty unless he gave his patient the benefit of it all, and the "shot-gun" prescription flourished at its best.

A natural reaction against this set in, and had for one of its first results the establishment of homeopathy by Hahnemann, near the end of the eighteenth century. The Hahnemann system was by no means new. For the most part it had its roots much further back. It was the natural result of the then existing theory of "vitalism."

Hahnemann believed that disease depends upon a perversion of the purely spiritual vital powers and is entirely immaterial in its nature. Logically, a thing spiritual could not be combated by material remedies, and, hence, Hahnemann turned to a spiritual power which he believed to be bound up in plants and liberated by dilution. This liberation of the principles exactly turned their action around, so that the action of his dilutions was, he stated, exactly the opposite of that of the concentrated drug, and could be used for the relief of such symptoms as the latter produced: *Similia similibus curantur.* This was the first tenet of Hahnemann. The second was that the nature of the disease being unseizable, it was not subject to treatment, but that only its symptoms can be treated. Hence, homeopathy, in so far as it follows the principles of its founder, has no place for the medical sciences, such as physiology, anatomy, pathology, or chemistry. Any one with an indexed book of symptoms and their remedies would be able to practice it without an elaborate study or preparation.

In marked contrast to the above is the third dictum: that the medicinal treatment must be supported by dietetic and hygienic measures.

The claims of homeopathy as a rational system hinge on the proof of the *similia similibus* theory. Most of its advocates seem to deny altogether the relevance of scientific testimony, and to base themselves purely on the slippery ground of empirical experience. Others, however, whilst they carefully neglect the great body of scientific experience which disproves their theory, seem very glad to avail themselves of the few experimental facts, which, through a variety of logical contortions and sophistications, can be twisted into a specious support. Hahnemann himself seems to have started from the observation that large doses of drugs produce the opposite effects from moderate doses. The correctness of this principle may be granted, for most cases. But it is a very unwarranted feat of logic to assume that infinitesimal doses must again cause effects opposite to those of moderate doses!

The more recent discovery of the effect of dilution on electrolytic dissociation, on ionization, has also been seized upon as illustrating homeopathy — quite disregarding the fact that the action depends on the number of ions rather than on the degree of ionization; and the further fact, that the majority of the substances employed in homeopathy are not electrolytes at all! These few examples may suffice.

Hahnemann's system was the natural outgrowth of his time. At present it is an anachronism, as his pupils are the first to acknowledge in practice, if not in words. But in his time Hahnemann accomplished considerable for medical science. . He called attention to the importance of diet, etc., when this was only too much neglected; but perhaps the principal use of homeopathy has been to show to rational medicine the fact that disease tends to recovery without any medical interference.

This was, indeed, the next step which medicine took — total emancipation from all drugs. This dates from the establishment of the Vienna school by van Swieten, in 1745. The strongest advocate of nihilism was Skoda (1805–1881), the founder of the methods of percussion and auscultation. Such nihilism was absolutely necessary at that time, just as periods of skepticism are necessary in philosophy, and mark steps in progress. The accumulated refuse was so great as to bury the good. The only way was to empty out the whole and begin anew. This was a necessity then, but now nihilism is as obsolete as the gun-shot prescription. He who proclaims it, simply proclaims his own ignorance and want of critical faculty.

The reestablishment of therapeutics, founded now upon reason, was thus aided by the very man who had attempted to destroy it. For he established physical methods of diagnosis, and demonstrated the effects of disease as they had never been demonstrated before, making it possible also to demonstrate the effect of remedies.

Then followed the isolation of active principles (led by the discovery of morphin in 1817), thus substituting the definite for the indefinite drugs. Finally followed animal experimentation, by means of which modern pharmacology has developed.

Rational therapeutics is now on a firm basis. But, at the same time, the mystic has also been further developed, not only in homeopathy, but also in the many forms of suggestion. The value of suggestive therapeutics proper cannot be denied. It is a strictly scientific method of treatment, and is employed in its milder forms by every physician as "the personal influence" and the "faith in doctor and medicine." It often constitutes all there is of merit in those medical fads which have accompanied medical science since the oldest time.

One of the most important preliminaries to the rational treatment of disease is that the physician should understand that he cannot make a patient well. That is exclusively nature's task. "Nature" inevitably tends to bring the organism back to its normal condition, and the task of the physician consists in directing his treatment in such a manner as to remove obstacles from nature's path. Just as the surgeon cannot cause the union of a broken bone, but can only put it in the most favorable condition for nature to perform this union,—*i. e.,* set it,—so the physician cannot cure heart disease. He may either remove the condition which causes it, if still present, or remove by digitalis, etc.. the factors which retard the cure; but in any case he must rely upon nature to perform the last, the really important act: viz., the permanent return to normal.

That nature not only puts the final touch upon every reparative process, but that she may take every step as well,—*i. e.,* that a patient may get well without any medical interference,—is too well known to require further discussion. The ways in which these processes of repair take place constitute one of the departments of pathology and medicine.

In the light of the above, it might well be asked: If nature is thus able to effect cures; if by far the greater number of diseases tend to spontaneous recovery, what is the function of the physician? Can he do anything but harm if he attempts to meddle with the great processes of nature? If he undertakes to aid, does he not really meddle? We must, in examining this question, lay the emphasis in the above sentence on "nature *tends* to effect a spontaneous cure." But nature is essentially blind in her workings. She works by general laws, which often do not take account of individual cases. Though we must recognize her processes as almost always the best under the given conditions, they may be greatly at fault quantitatively. Nature may do too much or too little. It is now conceded that fever, pain, inflammation, etc., are protective mechanisms; but when the fever becomes so high as to be in itself dangerous to life, when the pain is intolerable and constant, and persists after it is no longer needed; when inflammation spreads; then it is evident that the originally salutary process is becoming the reverse. That the processes of nature are often insufficient is evident from the fact that it does not in all cases effect a cure. Nature may sometimes be absolutely wrong; *e. g.*, in the desire for solid food in typhoid.

It is, then, the duty of the physician to judiciously modify the natural tendency, if he possesses the means of doing so. But he must do so wisely, or it were better not at all. He must understand the diseased condition; he must understand nature's way of meeting the difficulty; he must judge in what ways nature may be supported; and, finally, he must thoroughly understand the means at his command for the purpose — *i. e.,* pharmacology. As long as he is not clear in regard to these factors, he is merely groping in the dark, as likely at least to do harm as good. In this case expectant treatment is alone justifiable.

We see how from the above we can deduce a number of methods of treatment.

I. Expectant Treatment: i. e., the absence of any real attempt at treatment beyond hygiene, rest, diet, and other similar general measures; with the object of leaving the powers of nature free play. This should be employed in all cases where no better treatment is known; but, as has been said, it is usually within the province and power of the physician to support nature in her endeavor.

The expectant treatment must also be used when it is desired to let the disease progress to a certain point, if this is necessary for diagnosis. Thus, general treatment for primary syphilis is usually expectant, since no great benefit would result from immediate specific treatment, whereas the diagnosis would be greatly obscured thereby.

II. Symptomatic Treatment.— This is aimed at the symptoms of the disease without reference to their cause. This may be objectionable in some cases, indicated in others. In striking the symptoms one very often also strikes the disease. Again, the symptoms in themselves may be so objectionable or lead to such secondary results as to make their removal desirable. Pain, cough, and fever are all purely symptoms, and yet no one would refuse to treat them simply because unable to remove the root of the disorder. On the other hand, the symptoms may be very deceptive — a chill will not require external heat; a referred pain will not be relieved by local application of iodin to the place where it is felt.

In removing the symptoms the physician also deprives himself of the only index to the treatment of the underlying disorder. He must constantly be on his guard against believing himself successful when he has succeeded in removing one or several of the symptoms of the disease. In many cases the symptom may itself be salutary; in which case it would not do to remove it (*e. g.,* cough when there is hypersecretion of mucous; a certain amount of pain when rest is indicated in fracture).

It need scarcely be mentioned that it is not ethical to persuade a patient that he is being cured when he is in fact only being relieved of the symptoms.

III. Empirical Treatment.—This follows merely the dictates of experience without concerning itself about the reasons for these. While in the present state of our science it is still necessary to employ it only too often, it requires scarcely a thought to see how often it may be not only useless, but even injurious. Conditions which resemble each other very closely superficially may really be diametrically opposite, and may require very different treatment.

IV. Rational or Scientific Treatment.— While this makes use of the three preceding methods, it aims essentially to remove the cause of the disorder and to favorably influence its course. It presupposes a knowledge of both. cause and course, as well as a thorough acquaintance with the manner in which they may be influenced by remedial measures.

While it relies, on the one hand, on the science of pathology, etc., for the revelation of the nature of the disease, it requires equally accurate knowledge of the nature of the action of drugs: viz., scientific pharmacology.

THE RELATIVE IMPORTANCE OF THE DIFFERENT DRUGS.

Therapeutics is not yet in a stable condition: its theories are still in a state of development, and as they change, the use of the different drugs undergoes corresponding changes. It is therefore necessary for a student to have some knowledge of all the drugs which may be used, whether they are at present popular, or not. At the same time, many drugs have almost identical actions, and for the sake of simplicity, a considerable part of our materia medica could well be dispensed with. The beginner is often at a loss to make a proper selection of the most important drugs, to which his attention should be mainly directed. The following list — which is arranged in the same order in which the drugs are treated in this book — aims to enumerate those which are really indispensable.

List of most important drugs, from the therapeutic standpoint: Strychnin, Caffein, Morphin, Heroin, Cocain, Atropin, Pilocarpin, Physostigmin, Thyroid, Suprarenal, Apomorphin, Aconite, Quinin, Phenacetin or Acetanilid, Salicylate, Phenol, Creosote, Diphtheria Antitoxin, Alcohol, Ether, Chloral, Sulfonal, Amyl Nitrite, Trinitrin, Digitalis, Ergot, Normal Saline, $MgSO_4$, KBr, KI, NH_4Cl, $KC_2H_3O_2$, HCl, $NaHCO_3$, As_2O_3, $FeSO_4$, Fe_2Cl_6, Hg_2Cl_2, $HgCl_2$, Hg_2I_2, ZnO, $AgNO_3$, Bismuth subnitrate, Hexamethylenamin, Krameria, Gentiana, Asafetida, Mentha piperita, Rheum, Podophyllin, Aspidium, Santonin, Acacia, Oleum Olivæ, Petrolatum, Oleum Morrhuæ, Pepsinum.

CHAPTER VIII.

CONVULSANT SERIES.

A very large number of poisons are capable of producing convulsions; some by a direct excitation of the nervous centers; others indirectly, through asphyxia, etc. In the present chapter only those will be considered in which the convulsive action is direct and important. The series comprises three groups: strychnin, acting mainly on the spinal cord; picrotoxin, with its main action on the medulla; and caffein, which affects the entire central nervous system, and which has other actions of great therapeutic importance.

(A) STRYCHNIN GROUP.

Derivation.— The principal members of this group (strychnin, brucin) are derived from plants of the genus Strychnos, especially S. Ignatii and S. Nux Vomica.

Alkaloids with a strychnin-action are also found in opium (thebain); gelsemium (gelsemin); and physostigma (calaberin). These drugs however, also contain other alkaloids whose action is predominant; so that they cannot be counted in the strychnin group. The action of *tetanus toxin* resembles that of strychnin very closely.

II. SUMMARY OF ACTIONS.

1. Increased reflex irritability of the central nervous system, from below upward. The most prominent symptoms of this action consist in convulsions. These are accompanied and followed by central paralysis.
2. "Bitter effect" on the alimentary canal.

3. With direct application, a curare action on striped muscle, and paralysis of the superior cervical ganglion. High concentrations are toxic to all protoplasm.

III. DETAILS OF ACTION.

(A) Central Nervous System.— 1. Spinal Cord.— The principal symptom of strychnin-poisoning[1] is an increased reflex irritability of the spinal cord, shown most conspicuously by the production of tetanus. The animal, frog or mammal, after a short period of increased reflex excitability, is thrown into violent clonic spasms. (Spasms or convulsions are called clonic when they are intermittent, tonic when persistent.) There are sudden and violent contractions of all the muscles of the body, persisting for a few seconds or minutes; then there is complete relaxation, the animal showing all the signs of paralysis. After a few minutes the convulsions are repeated, to be again replaced by paralysis. With appropriate doses these phenomena may be repeated almost indefinitely (from eighteen to forty hours) with frogs, whereas mammals usually die after the first few convulsions.

With smaller doses, the paralysis disappears gradually. The animals, however, may again go into convulsions, and die, several hours after apparently complete recovery. Frogs may show a spasmodic condition for as long as ten days.

Location of the Tetanus.— A tetanus or spasm may conceivably be located in the muscle, nerve endings, spinal cord, medulla, brain, or sensory endings.

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[1] Exercise 39.

The *experimental distinction between these possible actions* forms a very interesting chapter of pharmacology, and illustrates very well the general methods of pharmacologic experimentation. The experiments can be carried out most conveniently on frogs;[1] but they can also be demonstrated on mammals.

Muscle and nerve endings may be excluded by section of the nerve-trunk. This stops the convulsions.

If the spasms in these structures had not ceased after section of the nerve, one could distinguish between them by the administration of curare. This would stop the contraction of the muscle if it had its origin in the stimulation of its endings, but not if it were located in the muscle-fibers.

Brain and Medulla.— These can be excluded by successive section or destruction. If division below the brain or medulla stop the convulsion, the seat must be in one of the structures above the divided point.

This is not the case with strychnin: Section of the medulla may indeed lessen the tetanus for a short time, by shock, but it soon returns to its former intensity. The brain and medulla are therefore not concerned in the convulsions. This leaves only the cord, and the sensory endings.

If the strychnin is injected into a leg which has been ligated, with the exception of the sciatic nerve, no convulsions occur. In this experiment, the strychnin can act on the sensory endings, but not on the cord, so that the absence of the tetanus shows that *the action is not on the sensory endings.* This conclusion is confirmed by other experimental methods. The *posterior root ganglia can also be excluded,* for if all the posterior roots are cut central to the ganglia, and one of the stumps is stimulated, a typical tetanus results. *The tetanizing action of strychnin must therefore be situated in the cord.*

It still remains *to distinguish between the motor and sensory cells of the cord.* To do this, Baglioni (1900) availed himself of the fact that impulses pass from the sensory cells of the anterior segments of the cord to the motor cells of the posterior segments; and vice versa. By destroying the circulation and applying strychnin locally to the exposed cord, it is therefore possible to make impulses pass either through a poisoned sensory cell to an unpoisoned motor cell; or through unpoisoned sensory to a poisoned motor cell. In figure 45 the strychnin is supposed to be restricted to the anterior half of the cord. The path ——— goes through a poisoned sensory to an unpoisoned motor cell; the path — — — — through an unpoisoned sensory to a poisoned motor cell. When the foreleg is stimulated in this frog, the hindleg participates in the convulsions. When the hindleg is stimulated, there is no convulsion. In other words, when the impulse passes through a poisoned sensory cell, convulsions ensue, whether the motor cell is poisoned or not; when the sensory cell is not poisoned, there is no convulsion, even though the motor cells are exposed to the poison. This justifies the conclusion that the *action of strychnin is on the sensory cells, not on the motor cells;* or at least, on some structure between the entrance of the sensory nerve into the cord, and the motor cell. The effect of strychnin on the medulla and on the special senses, in which no motor elements are involved, also favors the view that it acts selectively on the sensory elements.

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[1] Exercise 38.

The question now arises, whether the strychnin stimulation produces convulsions by originating new impulses, *i. e.*, by a direct excitation of the centers; or whether it acts merely by intensifying ordinary impulses. The question must be answered in favor of the latter view: *the action of strychnin consists in facilitating the passage of the nervous impulse through the sensory paths,*[1] so that very slight stimulation leads to exaggerated motor response.

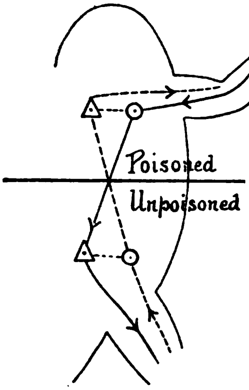

FIG. 45.— Diagram of Baglioni's Experiment.

Strychnin tetanus must be conceived as caused by the extensive spreading of reflexes on the application of small stimuli (a spreading which is not normally seen except after the very strongest stimulation).

The reflex character of the strychnin convulsions is shown by the fact that in slight degrees of strychnin-poisoning the convulsions do not occur spontaneously, but only upon stimulation. In very large doses the stimulation required may, indeed, be so small as not to be perceptible and the tetanus may bear an automatic character. But that reflexes are involved here is shown by the fact that the convulsions may be prevented by cutting off sensory impressions from the cord; *e. g.*, by placing a frog in a weak cocain solution, just strong enough to paralyze the sensory endings without producing central paralysis; or by dividing all the posterior roots.

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[1] The resistance may be lowered at three different points; in the cells, the endings, or the nerve-fibres of the spinal cord. There is reason to suppose that the fibres in the central nervous system are as resistant to poisons as the peripheral fibers, and that the action is therefore limited to either cells or endings.

The *nature of the stimulation* is of some importance.

The convulsions are only elicited by stimulation of certain paths, *i. e.*, by direct stimulation of a nerve, and by the special senses of sight, hearing, and especially touch, the latter being by far the most active. Direct stimulation of an exposed muscle or of the intestine is very much less efficient than stimulation of the skin. No matter how slight the stimulation, if it has any result at all, this is always maximal.

The effect is also influenced by the abruptness of the stimulation, a gradual stimulus, such as is produced by chemic irritation (acids) being less effective.

Whilst the experimental proof of the site of the action is essential in the study of every convulsant poison, a fairly accurate judgment may be formed by observing merely *the character of the convulsions.*

If the action is *on the muscle substance:* the effect may consist in an increased tonus (veratrin) or in fibrillary twitchings (physostigmin); on the *motor endings:* fibrillary twitchings (aconitin); on the *spinal cord* (strychnin): increased reflexes; abrupt movements; twitching of limbs; coördinated clonic spasms; opisthotonos (*i. e.*, body arched backward); adduction of hind-legs; on the *medulla* (Picrotoxin): the convulsions are cyclic: there is first a period of quiet; then sudden convulsions, the animal "bucking" or turning somersaults; abduction of hind-legs; emprosthotonus (body curved forward); reflexes vary with stages of cycle; pupils dilated. On the *brain:* The effects are as with the medulla, but there is an entire absence of reflexes, and no somersaults. On the *motor areas* (Epilepsy): The convulsions involve first isolated muscles, and then become incoordinated. On the *sensory endings* (irritants): Signs of pain; the movements are irregular and directed to the removal of the irritant.

The location of the tetanizing action of strychnin in the spinal cord is not only of experimental interest, but also of practical importance. It explains, for instance, why strychnin convulsions are abolished by curare, since curare blocks impulses from the cord to the muscles. Also, that strychnin has a stronger action on a paralyzed limb in those cases of paralysis in which the lesion is above the cord, for cutting off of the spinal cord from the brain always increases its reflex excitability.

The fact that strychnin in small doses increases the *tone of muscles* is also due to its heightening the reflex excitability of the spinal cord. Not only the convulsive centers, but other spinal centers are put in a condition more favorable to reflexes. It is in this way that strychnin is useful in *impotence* or in *paralysis of the bladder or other sphincters,* when these are due to lowered activity of their respective spinal centers.

The increased activity of the muscles brings about several secondary results: (1) *Pain:* Strychnin convulsions are extremely painful, just as any other form of muscle cramp.

Patients and animals very often utter a *sharp cry* at the beginning of a convulsion. This, like the cry of epilepsy, is not due to the pain, but to the sudden contraction of the expiratory muscles, for it often precedes the convulsions.

(2) *Increased metabolism:* An increased consumption of oxygen and increased output of CO_2, and an increased use of glycogen. (3) Tendency to *rise of blood pressure.* (4) Tendency to *quickening of the pulse* (which is counteracted by the stimulation of the vagus center). (5) Tendency to increase of *temperature,* which is counteracted by the dilation of the cutaneous vessels.

Effect of Convulsants on Temperature.[1]— All convulsant poisons (santonin, picrotoxin, strychnin) produce characteristic changes in heat regulation. Small doses cause increased heat loss and a slightly smaller heat production. Larger doses cause increased metabolism, through muscular action, and hence increased heat production, which is accompanied by a further increase of heat loss. Paralytic doses diminish the heat production very greatly. The *temperature* is accordingly variable: Small doses tend to lower it; moderate convulsive doses would increase it; paralytic doses lower it greatly. The heat loss is particularly conspicuous in small and young animals, whilst larger animals tend to show a rise of temperature, with moderate doses.

(6) *Asphyxia* by tetanic fixation of the respiratory muscles (later, also by the depression of the respiratory center). *This asphyxia brings with it* a venous condition of the blood and venous congestion of organs, lividity of the skin, protrusion of the eyeballs, dilated pupils, increase of the convulsions, and rise of blood pressure. These stimulant effects are soon replaced by paralysis of the same functions, and the animal dies in coma.

Asphyxia also causes *glycosuria.* The sugar of the blood rises, whilst the glycogen of the liver diminishes or disappears entirely.

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[1] Exercise 36.

Both the convulsant and the paralytic effects of asphyxia coincide with the actions of strychnin. Asphyxia is therefore often contributory to the fatal ending of strychnin poisoning, and may even be the main cause of death. *Life may therefore be prolonged or saved by artificial respiration,* especially if this is begun before the natural respiration has entirely ceased. The convulsions are also lessened.

The effect is partly due to the oxygenation of the blood, for the inhalation of oxygen is similarly beneficial. The rhythmic movements of artificial respiration are, however, also important; for it has been shown that artificial respiration prolongs life even when it is carried on in an atmosphere of pure hydrogen (Meltzer and Gies, 1903). It would seem that these movements have a reflex inhibitory effect on the convulsive centers. The view that the oxygenation of the blood causes an increased destruction of strychnin lacks sufficient experimental support.

The convulsions of brucin, thebain, and caffein are also lessened by artificial respiration, whilst those produced by picrotoxin and nicotin (which do not require reflex stimulation) are not affected.

2. Effect of Strychnin on the Medullary Centers.— Strychnin causes a stimulation, followed by depression, of the medullary centers, particularly the respiratory and vasomotor center. The stimulation, like that of the spinal cord, is produced by increased reflex excitability.

Effect on the Circulation.— The action of strychnin on the circulation involves a number of factors: The direct action of strychnin on the vasomotor and vagus centers, and the indirect effect of the convulsions, of respiratory movements, and of asphyxia. There is also a direct action on the cardiac muscle.

Small (therapeutic) doses have only a very slight effect on the circulation, in normal animals.

There is at the best a rise of blood-pressure of some twenty millimeters of mercury; the pulse may be somewhat slowed. This effect is due to a slight central vasomotor stimulation; the heart muscle is not affected. Often there is absolutely no effect. Sphygmo-manometric observations on the normal human subject, in typhoid fever, and in many other conditions, have also been negative, for the most part (Cabot, 1904).

Amongst clinicians, however, the opinion prevails very widely, that strychnin is a "*cardiac stimulant.*" This clinical term does not necessarily imply that the drug stimulates the heart directly; but merely that it improves the pulse. (The expression is used so loosely, that the student is advised to discard it altogether.) In the case of strychnin, this would be an indirect result of the rise of blood-pressure, if it occurred at all. In view of the practically negative results of all exact methods of observation, the claimed beneficial effect of ordinary doses of strychnin on the circulation must be considered as not proven. Nevertheless, it is conceivable that, under special conditions which have not been sufficiently investigated, the strychnin does have some effect — perhaps indirectly, by improving the respiration; or by altering the distribution of blood, without affecting the general blood-pressure. These assumptions are purely hypothetical, and need only be invoked when the beneficial effect is universally conceded by clinicians. As these doses of strychnin can do little harm, except perhaps in arteriosclerosis, there can be no objection to their trial.

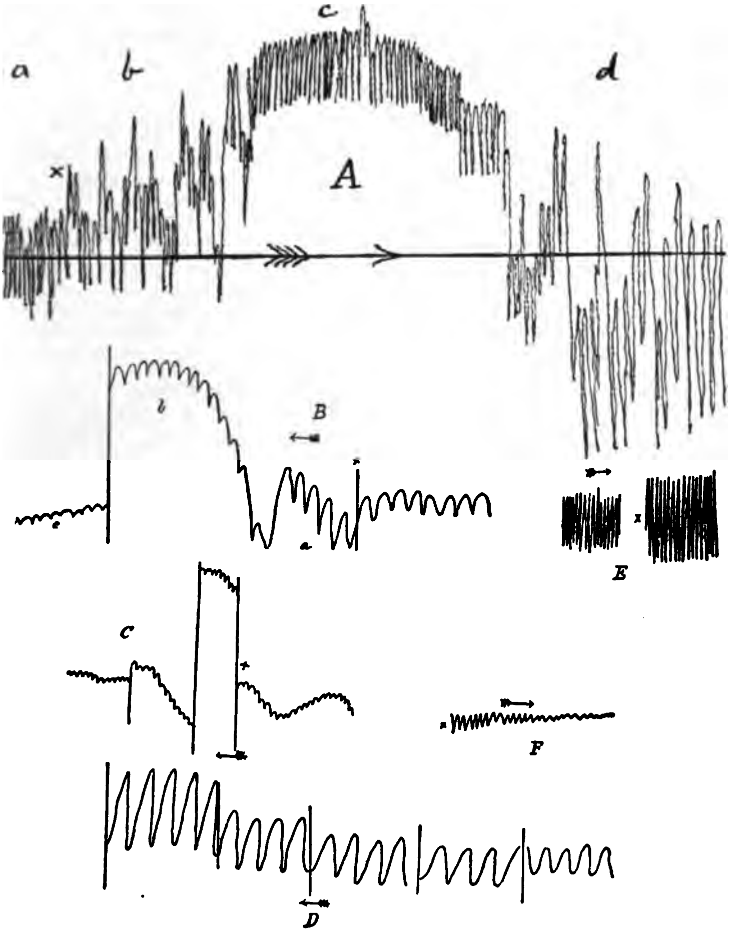

Fig. 46. *Effects of Strychnin:* The action begins at ×. *A, B,* and *C* are carotid pressure tracings from dogs. *A* and *B* are explained in the text. *C,* Shows rise of pressure after *complete curare paralysis; i. e.,* direct vasomotor stimulation. *D,* Respiratory tracing, dog (tracheal cannula to tambour by T-piece). *E* and *F,* Tracings from isolated heart (after Hedbom): *E,* Stimulant effects; *F,* paralytic effects.

Whilst small doses of strychnin have but little effect on the circulation, *convulsive doses* cause very conspicuous changes; especially a large rise of blood pressure, due to central vasomotor stimulation, produced mainly by the direct action of strychnin on the center; but aided by the convulsions and asphyxia. This is followed by vasomotor depression.

These effects are synchronous with the convulsions: the typical course is shown in figure 46 A: with the onset of the *irregular spasms* at (b) the mean pressure rises (central vasomotor stimulation), the heart being slowed and strengthened (central vagus stimulation; see also Fig. 46 B. a.). During the *tetanus* (A. c.), the pressure is very high (intense stimulation of vasomotor center), the heart beats are faster and smaller (reflex vagus depression, mainly through muscular exertion; see also B. b.). *As the tetanus disappears* (A. d.) the pressure falls below normal (central vasomotor paralysis), and the heart beats become very strong and slow (intense vagus stimulation, mainly asphyxial). The phenomena A b to d are repeated during each spasm.

As death approaches, and the respiration stops permanently, the pressure remains low, and the heart beats rapidly but weakly (Fig. B. c.; total paralysis of vasomotor and vagus centers), and finally stops. After a time, there may be a few slow, strong beats, as in figure 47 h.

This description applies almost equally well to the effects of convulsions, produced by any other cause; and particularly to asphyxia (see Fig. 47). These are both present in strychnin poisoning, and must be contributory factors. However, they are not the main cause of the rise of blood-pressure; for this occurs when convulsions are excluded by complete curarization (Fig. 46C); and when asphyxia is prevented by artificial respiration. Only the portion (d), of the tracing 46A, is due entirely to asphyxial vagus stimulation.

In curarized animals, the rise in blood pressure occurs spasmodically, and can be brought on by reflex stimulation, just like the convulsions in ordinary animals. The dose required to produce the convulsant and the vasomotor action are also identical. This supports the view that the action of strychnin on the medullary centers is essentially identical with its action on the spinal centers.

Action of Strychnin on the Heart.— Strychnin also has some action on the heart, at first stimulant; later and with larger doses, depressant. (Fig. 46, E. and F.) The effects are only seen when high concentrations are perfused directly through the heart. They are not at all concerned in the therapeutic action, and probably not even in the toxic effect. Strychnin is therefor not a cardiac stimulant in the pharmacologic sense.

The *spinal vasomotor centers* are also stimulated, for injection of strychnin raises the pressure after section of the cervical cord. (The existence of spinal vasomotor centers has been denied.)

The Respiratory Center.— This is stimulated (Fig. 46, *D*) by strychnin both directly and reflexly through increase of muscular work.

The direct increase in the excitability of the respiratory center is very important therapeutically. The activity of this center is normally extremely variable, and as a result of disease — *e. g.*, asthma — or of drugs, the irritability of the center may be so depressed as to cause absolute failure of respiration. Strychnin removes this depression and enables the same stimuli to effect much larger results, and in this way tides over a danger.

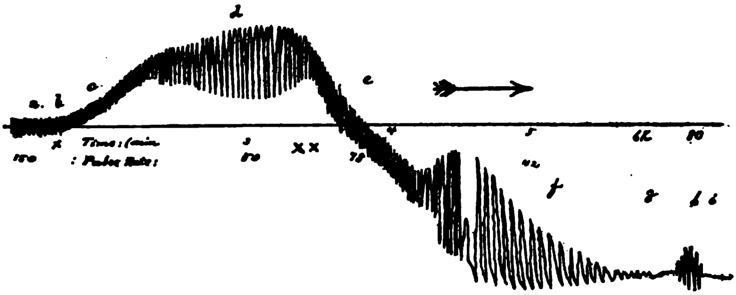

Figure 47. Asphyxia on blood-pressure (Dog). The trachea was tied at X. The respiratory movements are at first exaggerated, but become shallow, and stop at XX. The heart stops at (g); but it often gives a few isolated beats (h) after having stopped for several minutes. (b to c): central vasomotor stimulation; (e to i): depression of vasomotor center; (d to g): central vagus stimulation, more pronounced toward the end.

The variable excitability of the respiratory center explains why the results obtained by faultless experiments are not always uniform. In fact, the useful stimulating effect of strychnin has been absolutely denied by some. But most experimenters and clinical observers agree that there is such a stimulation by strychnin and its group, as also by caffein, ammonia, atropin, and camphor.

Paralytic Effects.— The paralysis of the medullary centers and spinal cord is partly masked by the convulsions, but shows in the intervals and toward the end. It is the usual cause of death in mammals, unless this takes place during respiratory spasm. The respiratory center, vasomotor center, vagus center, and the cardiac muscle fail in this order. Exhaustion, asphyxia, and the direct depressant action of strychnin are all concerned in the paralysis.

That exhaustion is an important contributory factor is shown by the fact that life may be greatly prolonged by preventing the convulsions through chloral or curare. The prolongation of life by artificial respiration shows the contributory action of asphyxia. However, animals die from large doses of strychnin, when exhaustion and asphyxia are both excluded, in the manner indicated.

There seems considerable reason to believe that in the frog the paralysis of the central nervous system is caused largely by the failure of the circulation through cardiac paralysis, but this is not the sole cause, for the heart is often still beating when the reflexes have disappeared. In the case of mammals death usually occurs before the heart has stopped.

It must be concluded that large doses of strychnin exert a *direct depressant action on the medulla and cord.* It is doubtful whether small doses produce any depression; with moderate doses, it is obscured by the stimulation, the two conditions being present at the same time. It is not known whether the depression is merely a consequence of the stimulation, or whether it is an independent action.

It is important to bear in mind that the convulsions are not the dangerous element in strychnin-poisoning, but the paralysis.

Tetanus alone is not such a dangerous condition. Thus, tetanus quite as violent as that of strychnin has been produced, *e. g.*, by camphor, without being fatal, and the very severe convulsions of traumatic tetanus may last for weeks, whereas large doses of strychnin may kill after a single twitch or even without any signs of convulsions (death may then, however, be due to cardiac paralysis).

This is of great therapeutic importance, since it teaches that remedial measures must be directed not only against the convulsions, as against the subsequent paralysis.

3. The effects upon the **brain** have not been sufficiently investigated. This much is certain, that they are not very great. There is no evidence that the *motor or psychic areas* are more excitable. Consciousness is not lost until the asphyxial coma.

Among the **special senses** there is a well-marked *increase in the sharpness and field of vision for all colors*, and in the olfactory sense, whilst the sense of touch is but slightly affected. The action is central; in the eye perhaps also on the retinal ganglion cells.

(B) Peripheral Actions.— When used systemically, strychnin has *no action on nerve-fibers, nor striped nor un-*

striped muscle, nor sensory end-organs. Very large doses, however, lessen the excitability of the latter in the frog. It has a curare action on the endings of striped muscles.

This may be seen in the frog, but it develops too late to show in mammals. Both strychnin and brucin paralyze the superior cervical ganglion. It has not been investigated whether this extends as well to the other sympathetic ganglia. The effect upon the heart has already been mentioned. Whether this effect is on the muscle-fibers or nerve endings cannot now be stated with certainty, but it is probably muscular.

Alimentary Canal.— Strychnin is often of great benefit in chronic gastric and intestinal catarrh. It shares this action with all other bitter substances (see Chapter XXX). For this local effect, the Galenic preparations of nux vomica are superior to the pure alkaloid, since they are not so quickly absorbed.

Strychnin is also useful in *atonic constipation*, especially if it is used in conjunction with mild cathartics. The effect is perhaps explained by an increased tone of the centers which control intestinal movements.

Action on Invertebrates.— The effects of strychnin upon animals devoid of a central nervous system have not been sufficiently studied. All those possessing nervous structures are affected by it. Ameboid movements, as also gas formation by yeast, etc., are inhibited, but much larger doses are necessary than are required of quinin.

IV. ABSORPTION, ETC.

Strychnin is readily and quickly absorbed, mainly from the intestine. It is probable that the stomach partakes in the absorption in man, although this is not the case in the rabbit. The **excretion** begins quickly, but lasts for a long time (2 to 8 days). It takes place by sweat, saliva, bile, and especially urine.

Fate.— The excreted strychnin is unchanged. Part of the poison, however, undergoes destruction, probably oxidation, in the body. The poison is retained for a long time in the liver and central nervous system. It is not destroyed in the alimentary canal (Hatcher, 1904).

If strychnin is injected into the ligatured limb of a guinea pig, the toxic effect is considerably diminished when the poison is admitted to the circulation after several hours, by the removal of the ligature.

This is due to the very slow absorption of the strychnin through the obstructed circulation; a considerable portion of the strychnin disappearing (by elimination or destruction) whilst the ligature is intact.

Susceptibility.— *Continued administration* of strychnin does not lead to tolerance, but seems rather to increase the susceptibility to its action.

Children are comparatively insusceptible, whereas it is a dangerous poison for old people, on account of the frequent existence of atheroma or fatty heart, leading to rupture through the increased blood-pressure.

Different animals show a varying degree of susceptibility. With subcutaneous administration, man, cats, and dogs require about the same dose, per kilogram, to produce a fatal effect; rabbits are slightly more susceptible. Guinea pigs and frogs require about 6 times, and snakes 18 times, this dose. With the frog, the spasms appear with one-sixth the fatal dose; with the guinea, they only set in when at least 95% of the fatal dose has been given.

V. DIFFERENCES IN THE NUMBERS OF THE SERIES.

The description of the actions of strychnin applies also to *brucin, thebain, gelsemin,* and *calabarin.* Brucin occurs with strychnin in nux vomica; its action is much weaker, the ratio varying somewhat with different animals. The paralytic and curare effects are comparatively more pronounced, so that brucin is less useful therapeutically.

Tetanus toxin also produces a convulsant action on the spinal cord which is practically identical with that of strychnin. The paralytic action is less pronounced. The action developes more slowly (on account of the slow absorption, and probably by the existence of an incubation period) and, if the introduction of the toxin occurs by a wound, the tetanus is at first localized, and spreads only in the course of some days. This is also due to the slow distribution of the toxin, which appears to be conveyed to the spinal cord along the nerves. Another important difference is that tetanus toxin leads to the producduction of an antitoxin.

Relation to Other Groups.— By its action on the central nervous system, strychnin resembles *caffein* and *picrotoxin,* the difference consisting in the portion of the central nervous system mainly affected. The increased irritability of the spinal cord connects it with *morphin,* its action on the endings of the striped muscle with *curare.* (A derivative of strychnin, methyl-strychnin, is a member of the curare group.) The action on the cervical sympathetic ganglion is allied to that of *nicotin.* The cardiac paralysis is common to many poisons.

VI. TOXICOLOGY.

Time of Appearance of Symptoms.— The symptoms do not often appear before fifteen minutes, nor are they often delayed beyond half an hour, but in one case an hour and three-quarters elapsed before the symptoms began. The time will depend upon individual differences, upon the manner of introduction,— if into the stomach, whether this is full or empty, and upon the nature of the food, if any is present,— upon the place of introduction (hypodermically, etc.), and upon the preparation of the poison employed. The alkaloid will act faster than the tincture, and these, again, faster than pills.

First Symptoms.— The symptoms may start with a feeling of uneasiness and a heightened reflex irritability (nervousness); then comes a sensation of tightening and drawing in the lower jaw, or there may be a twitching of the little finger. These symptoms are the most that should be produced with therapeutic application.

In case any portion of the body is paralyzed from a high lesion, this part may be the first to show the spasms.

Advanced Symptoms.— With large doses these prodromal symptoms are usually absent, and the attack often begins suddenly, with a cry or shriek, which is usually caused mechanically by convulsive movements rather than by pain. This is followed very quickly by the characteristic convulsions. The patient is thrown into general convulsions, at first clonic and then tonic. Opisthotonos [1] results from the contraction of the extensors. The patient will touch the ground with his head and feet, the rest of the body being arched above the floor. The feet are curved inward. These conditions do not persist, but pass into clonic spasms and soon an intermission ensues.

The respiration during the attack is at first labored and dyspneic, and then ceases by the spasmodic contraction of the diaphragm. The abdomen and chest may become as stiff as a board. The patient may foam at the mouth on account of the disturbed respiration. The interference with the circulation and the pressure on the abdominal viscera, aided by the stimulation of the respective medullary centers, may lead to purging and vomiting. Lock-jaw and risus sardonicus may occur later. The interference with the respiration leads to asphyxia, and this to cyanosis, dilatation of the pupils, and later coma. The pulse is small and tense. The patient is perfectly conscious and usually suffers excruciating pain. In a few cases this may be absent on account of th eanesthetic effects of asphyxia. Great thirst is a common symptom.

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[1] In *Opisthotonos*, the body is arched backward; in *emprosthotonos*, forward.

These spasms are interrupted by *intermissions,* during which the stimulation symptoms disappear entirely and are supplanted by general depression. Suddenly the attack is repeated as before. The number of seizures is variable. Three or four are usually fatal. The duration of the spasms and of the intervals differs according to the severity of the poisoning. They become shorter toward death.

Death.— The patient usually dies in ten to thirty minutes after the first attack, either during a spasm or in the interval: if the former, through fixation of the respiratory muscles; if the latter, through paralysis of the medullary centers. Death by strychnin is characterized by early and often persistent rigor. (This is common to all forms of convulsions and is perhaps due to the increased production of acid.) The postmortem appearances are those of asphyxia and violent convulsions: venous congestion, often hyperemia of the central nervous system, and small hemorrhages; in a few cases hyperemia of the alimentary tract.

Differential Diagnosis of Strychnin-poisoning.— Strychnin tetanus may be confused with traumatic tetanus, spinal meningitis, epilepsy, or hysteria. *Traumatic tetanus* is characterized by previous malaise and slow development. The convulsions begin in the jaw. The muscles remain rigid in the intermission. The course is comparatively slow. Strychnin tetanus may also begin in the jaw, but not as markedly. In rare cases of strychnin poisoning the muscles also preserve their rigidity during the interval, so that the diagnosis is sometimes impossible. When in doubt, strychnin treatment should be used, as it is beneficial in all similar conditions. The course of the case will clear up the diagnosis.

In *spinal meningitis* the diagnosis may be made by the fever and history, and signs of injury to the vertebræ can generally be discovered. *Epilepsy* differs by the loss of consciousness; the reflexes are normal. In certain cases of *hysteria* the diagnosis may be impossible. Such cases should also be treated as for strychnin.

Treatment of Strychnin-poisoning.[1]— *Chemic and Emetic.* — This must be very prompt on account of the rapid absorption.

Permanganate or iodin (see p. 90) are preferred; tannin may be used, but not in the form of coffee.

Evacuation may be employed in *mild cases.* Emetics act too slowly and are too depressing, so that the stomach-tube would be preferred, using the chemic antidotes by lavage. If the symptoms are *severe,* evacuation would be too late to do any good, and could even be *harmful* by starting the convulsions. It should never be used if the patient struggles, since *perfect quiet is of the greatest importance.*

For *physiologic treatment,* the most useful antidotes are the members of the group of hydrocarbon narcotics: chloral, paraldehyd, or chloroform. They have all been advised. Chloral is given in doses of 2 Gm. (½ drachm), with the addition of another gram (15 grains) after half an hour or longer, as necessary. There is always the danger in giving this, that its paralytic effects may coincide with those of the strychnin, and thus increase the danger. For this reason *chloroform* is considered the best, since its action can be very largely controlled. *Morphin* should be avoided, and only used in emergency. Its effect upon the brain is, of course, antidotal to the strychnin, but this is of little importance, and on the other hand, it is likely to increase the reflex excitability of the spinal cord and thus add its effect to that of strychnin. Its depressing action on the respiration is also certainly undesirable. Nicotin was at one time recommended, but thorough tests have shown that it is useless, as might well be predicted from its action. Pilocarpin is also useless.

Artificial respiration, as well as the inhalation of oxygen, should be begun early, since this has been proved to be a most efficient treatment.

It is claimed as a result of animal experiments that the application of external heat decreases the mortality.

The *fatal dose* is stated as ½ to 1½ grains (0.030 to 0.1 Gm.), the former being the smallest fatal quantity recorded, but $^1/_{12}$ grain in a woman has given violent results. However, even 4 grains have been recovered from in cases where appropriate treatment was used. As much as ⅔ grains

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[1] Consult Exercise 29.

(0.04 Gm.) is sometimes administered three times a day for therapeutic purposes: This practice is distinctly dangerous.

VII. THERAPEUTICS.

The principal effect of strychnin is upon the **spinal centers,** and this is made use of in various ways:

1. *General Tonic.*— Its tonic effect may be explained in two ways. First, by its producing an increase in the muscular tone. This increase of tone produces a more healthy feeling in the patient. Secondly, its effect upon the alimentary canal improves the appetite and digestion.

Consequently strychnin as a tonic should be given in the form of the preparations of nux vomica, the tincture being especially desirable. It is used in this way against marasmus, tuberculosis, chronic gastric or intestinal catarrh, etc.

2. *Paralytic Disorders.*— We repeat that strychnin only increases the excitability of existing structures. It cannot, therefore, be of any use in organic lesions of the cord. It may be of use in *functional* lowering of the activity of the cord,— *e. g.,* lead-poisoning, or sometimes in diphtheritic paralysis. It is especially useful in nervous lesions above the cord;

For, by stimulating the latter, it will preserve the tone, and, consequently, the nutrition of the muscles, and in this way may temporarily prevent their atrophy while the higher lesion is being repaired. For this purpose it will give the best results when used conjointly with massage and electricity. In some way it also lessens the pain in older paralyses.

3. *Other Reflex Spinal Centers.*— The lower centers of the cord, especially the sphincters of the bladder and rectum, are put into better condition by strychnin, and it is, therefore, useful in certain forms of incontinence of the feces and urine.

Incontinence of the urine may also be due to overaction of the detrusor urini, in which case atropin would be indicated.

The stimulation of the spinal cord also explains its effects in impotence.

4. The stimulant effects of strychnin on the **medullary centers** is utilized in conditions in which these are depressed; *i. e.,* in shock and collapse. Opinions as to its value differ.

These conditions are characterized by depression of the vasomotor, respiratory and vagus centers, *i. e.,* by rapid soft pulse and slow or shallow respiration. The phenomena are precisely the opposite of those of the typical effects of convulsive doses of strychnin. However, these large doses are not applicable, for the stimulation is succeeded by depression which adds itself to the exciting collapse, and proves promptly fatal.

The doubtful effect of therapeutic doses has been discussed on page 148. Useful results have been claimed in *surgical collapse,* at least in the milder cases;[1] in the collapse of *fevers;* in poisoning by *alcohol, anesthesia, the coal-tar derivatives,* etc. Recent experiments suggest that it may be useful to administer strychnin just before *anesthesia,* as it lessens the tendency to respiratory paralysis, without interfering with the anesthetic action. Very good results are claimed in *snake-poisoning.* Nux vomica has long been used by the natives of Ceylon for this purpose.

Strychnin is not so useful against depression by morphin-poisoning, for the same reason that prohibits morphin as an antidote in strychnin.

Those who regard sea-sickness as a collapse condition, have also employed it here, but its benefits are doubtful.

Strychnin may also be beneficial in *circumscribed vasomotor disturbances, e. g.,* in hemicrania. *It should not be used in heart diseases;* for if it has any action, it increases the work of the heart.

5. The useful effect of *strychnin* in acute *alcoholic poisoning* has suggested its employment in the chronic form.

Its usefulness here will vary according as to whether there is increased or diminished excitability of the cord, either of which may exist. In the latter case it is indicated, both on account of the greater relaxation of the muscles, and the gastritis. In the former it would be useful only as an appetizer, an effect which may be attained equally well by simple bitters (see Chap. XXX, A) without further increasing the spinal irritability.

6. The action of strychnin on the *respiratory center* is much more certain than its vasomotor effect. It has been found useful in all cases of respiratory failure, whether by direct depression or by fatigue of the center. When death seems imminent, it is justifiable to push the strychnin until twitching of the finger-tips occurs. It should never be continued beyond this stage, for the danger of producing strychnin paralysis is great.

We need only allude to the use of strychnin in *diminished visual activity.* It undoubtedly improves this, but its effects are only temporary.

A dose of 2 to 3 mg. is required to produce this effect. The action may also be obtained by the application of a 1% solution to the cornea.

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[1] In profound surgical shock, the vasomotor center is paralyzed so completely that it does not respond even temporarily to tetanic doses of strychnin.

Strychnin is stated to be occasionally effective in reducing the polyuria of *diabetes insipidus*. There is no pharmacologic explanation for this action, if it exists.

On the whole, *strychnin must be looked upon only as a temporary remedy*. It must be remembered that it does not in any way permanently improve the condition of the central nervous system, nor does it increase any of the functions except the reflex irritability. It is doubtful whether the permanent maintenance of this artificially raised irritability is ever of benefit. But that its temporary action in bridging over the time required for reparative processes is extremely useful, belongs to the best established facts of modern therapeutics.

VIII. MATERIA MEDICA.[1]

Nux Vomica (U. S. P., B. P.).—The seed of *Strychnos Nux Vomica*, Loganiaceæ, East Indies.

Contains about 2.5% of alkaloids, of which ⅓ to ½ is strychnin (not less than 1.25% U. S. P.), and the rest mainly brucin. Tannin, fat, gum, etc., are also present.

The drug was unknown to the ancients, and was probably introduced by the Arabs. The first good description occurs in 1540. Strychnin was discovered in 1818.

The bark contains the same principles in less amount, but relatively more brucin. It was formerly found in commerce under the name of "false angostura." Several arrow poisons are also derived from the genus Strychnos, especially the Upas Tieuté from Java. Some of the strychnos species do not contain any active principle.

Nux vomica also contains a small quantity of a third alkaloid, igasurin, which has not been very greatly studied, but which seems similar to strychnin.

Dose: 0.03 to 0.3 Gm. (½ to 5 grs.) (0.065 Gm. = 1 grain, U. S. P.).

Preparations (all miscible with water or alcohol. Made with three-quarter alcohol and acidulated):

- *Tinctura Nucis Vomicæ,* U. S. P. (10% = 0.1% strychnin), B. P.: 0.22% alkaloids. *Dose:* 0.3 to 1.2 c. c. (5 to 20 ♏) (0.6 c. c. = 10 ♏, U. S. P.).
- *Fluidextractum Nucis Vomicæ,* U. S. P.: 1% strychnin. *Dose:* 0.05 to 0.25 c. c. (1 to 4♏) (0.05 c. c. = 1 ♏, U. S. P.).
- *Extractum Nucis Vomicæ,* U. S. P. and B. P.: 5% strychnin, U. S. P. *Dose:* 0.01 to 0.06 Gm. (1/6 to 1 gr.) (0.015 Gm. = ¼ grain).

* **Ignatia.**— The seed of Strychnos Ignatia, Philippines.

Strychnin, 0.5% to 1.5%. Brucin, 0.5% to 1.4%. Tannin, fat, gum.

Dose: 0.03 to 0.2 Gm. (½ to 3 grs.).

Strychnina (U. S. P., B. P.).— $C_{21}H_{22}N_2O_2$ — Alkaloid derived from plants of the family Loganiaceæ. Soluble in 6,400 parts of water, 110 alcohol, 5,500 ether, 6 chloroform. Strychnin and its salts occur as colorless crystals or white powders. The taste is intensely bitter, perceptible in 1 : 700,000. Strychnin salts have the usual alkaloidal incompatibilities, and are also precipitated by iodids and bromids. Their *dose* is from 1 to 5 mg. ($^1/_{60}$ to $^1/_{12}$ gr.) (1 mg. = $^1/_{64}$ gr., U. S. P.).

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[1] Study Materia Medica Lesson 18.

* Not official.

The following salts are official:

		1 part soluble in water	1 part soluble in alcohol
Sulphate (U. S. P., B. P.),	$Str._2H_2SO_4 + 5H_2O$	31	65
Nitrate (U. S. P.),	$Str. HNO_3$	42	120
Hydrochlorid (B. P.),	Str. HCl	60	

Preparations:

Ferri et Strychninæ Citras (U. S. P.): 1% strychnin. *Dose:* 0.06 to 0.3 Gm. (1 to 5 grs.) (0.125 Gm. = 2 grains, U. S. P.).

Liquor Strychnini Hydrochloridi (B. P.): (1%.) *Dose:* 0.1 to 0.3 c.c. (2 to 5 ♏).

Elixir Ferri, Quininæ et Strychninæ Phosphatum (U. S. P.).

Glyceritum Ferri, Quininæ et Strychninæ Phosphatum (U. S. P.).

The *dose* = *Elixir:* 4 c.c. = 13. *Glyceritum:* 1 c.c. = 15 ♏.

Contains:	milligrams.	grains.	milligrams.	grains.
Strychnin	1.5	$^1/_{45}$	0.8	$^1/_{80}$
Quinin	35.	½	104.	1½
Ferri Phosphate....	70.	1	80.	1$^1/_5$

**Liquor Strychninæ Acetatis*, N. F. (Hall's solution): 0.2% (acidulated).

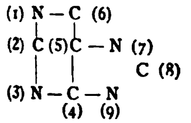
* **Brucin,** $C_{23}H_{26}N_2O_4$.—*Dose:* 5 to 30 mg. ($^1/_{12}$ to ½ gr.).

(B) CAFFEIN GROUP.

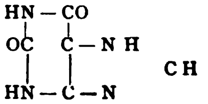
I. MEMBERS.

The members of this group are chemic derivatives of *purin,* or of xanthin (= dioxypurin). They exist in plants; as products of metabolism in animals (uric acid, guanin, adenin, hypoxanthin, heteroxanthin, paraxanthin, etc.); and can also be obtained synthetically.

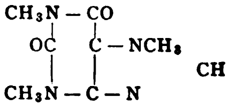
The composition of caffein is shown by the following structural formulæ (Emil Fischer):



PURIN



XANTHIN



Xanthin is derived from purin by the introduction of two oxygenatoms in the positions (2) and (6); and four H atoms in the positions (1), (3), (7), and (8). The first three may be replaced by methyl (CH_3), as in caffein[1] (trimethyl xanthin). Three dimethyl xanthin can exist: 1.3 (*Theophyllin*); 1.7 (*Paraxanthin*); and 3.7 (*Theobromin*).

All the soluble xanthin derivations exhibit the actions of the group to some degree.

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[1] The alkaloid of tea, formerly called *thein,* is identical with caffein.

The therapeutically most important members, caffein and theobromin, are found in plants of at least six families, which are scattered over many portions of the globe, and have usually been discovered and consumed by the natives. A list of the most important will be found under the materia medica.

II. SUMMARY OF ACTIONS.

1. Increase of the reflex irritability of the central nervous system from above downward, leading to a stimulation of the psychic area, then of the vasomotor and respiratory centers, and later to heightened reflexes and tetanic convulsions. In large doses this stimulation is followed by paralysis.

2. Increased ease of muscular contraction, progressing to loss of elasticity and to rigor (with skeletal and cardiac muscles).

3. Diuresis, probably by direct stimulation of the renal epithelium.

III. DETAILS OF ACTION.

(A) Central Nervous System.—1. The members of the series lead to a heightening of nervous activity, first shown in the **higher psychic functions.** This is most prominent with caffein, other members showing a more conspicuous paralysis.

There is a clearer and quicker flow of thought, disappearance of drowsiness, more sustained intellectual effort, more efficient appreciation of sensory influences of all kinds, especially in fatigue, and more perfect association of ideas.

With larger doses (0.5 to 1.5 Gm.) this passes into wakefulness and restlessness, vertigo, headache, and tinnitus aurium. With extremely large doses this may pass into delirium, and finally coma.

In lower mammals the cerebral effect is shown by restlessness. In the frog there are no symptoms referable to the brain.

2. Action on the Medullary Centers.— The effects of caffein on the medulla resemble closely those of strychnin. The stimulation is on the whole weaker, but more prolonged. The vasomotor stimulation especially is less pronounced. The vagus, and particularly the respiratory stimulation (Figs. 48 and 50 D), are relatively more prominent. The subsequent depression of the centers is less marked, even when large doses are used. (The effects on the vasomotor and vagus centers will be described in detail in connection with the circulation.)

3. **Spinal Cord.**— The effects upon the spinal cord also resemble strychnin, except that they are very much smaller and occur only with relatively large doses. There is the same increased reflex irritability, then tremors, and finally tetanus. This tetanus shows the same intermittent character as that of strychnin, and also involves the respiratory muscles in the same manner. It occurs both in mammals and frogs.

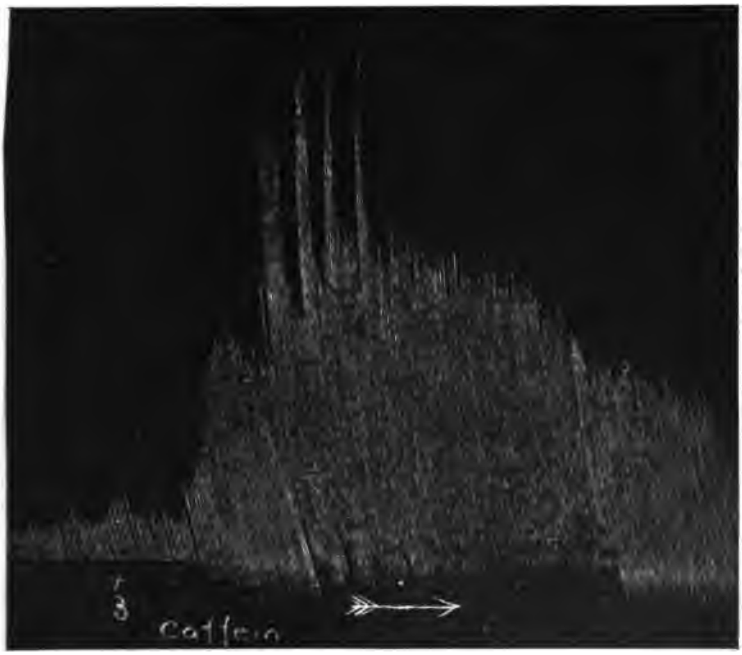

Fig. 48.— Effect of caffein on respiration (dog) in half natural size (taken from intact chest.

There is a difference in the reaction of *different species of frogs* to caffein. The esculenta is thrown into typical tetanus, whereas the temporaria goes primarily into rigor. The distinction is, however, quantitative rather than qualitative, since large doses will cause primary rigor in the esculenta also.

It rests upon a greater tendency to rigor existing in the muscles of the temporaria, for these are also more subject to other forms of rigor.

Caffein is, therefore, a striking illustration of the different effects which may be observed on the intact animal, since it may produce in frogs death in three different ways according to the strength and manner of its administration: The frog may die without any symptoms, through total collapse from cardiac paralysis, or it may be thrown into spasms through the stimulation of the spinal cord, or it may be overtaken by rigor through the action on the muscles.

The *tetanus,* like that of strychnin, is located in the spinal cord.

This tetanus is the only symptom with frogs. The dose required for mammals is considerably larger than that necessary to give a vasomotor, cardiac, or diuretic effect. Whereas for the latter 20 mg. per kilo are ample, 20 mg. will only cause tremors, and convulsions will not develop until 80 mg. have been given. Still larger doses paralyze the heart or the whole central nervous system.

In the intact frog the paralysis of the cord is obscured by the rigor. It can be demonstrated by ligating a leg exclusive of the nerve, when caffein will destroy its reflexes, although the muscles are still excitable.

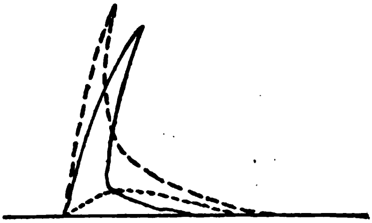

Fig. 49.—*Effect of Caffein on Gastrocnemius muscle of frog,* ——— normal tracing; — — — after five minutes in 1:10000 caffein solution; . . . in 1:1000 solution.

(B) The Effect on Skeletal Muscles.—(See Fig. 49 and Exercise 45). Caffein increases the contractility of all forms of muscle. Small doses increase the functional activity of the skeletal muscle, in all its phases: a lesser stimulation will suffice to produce contraction; the height and rapidity of contraction are greater, a larger weight can be lifted; fatigue is lessened, and a greater amount of work can be performed. Somewhat larger doses have the opposite effect. This is shown in a lengthening of the contraction very similar to that produced by fatigue; *i. e.*, the lengthening shows at first in the relaxation, later in the contraction as well. The other phenomena of fatigue are also present: The height of the contraction is less, the maximal load is smaller, and the muscle is exhausted more quickly by tetanus than is a normal muscle.

The contraction then becomes smaller and smaller, and the muscle gradually passes into rigor.

This increase and diminution of the functions bears so striking a resemblance to the phenomena of work and fatigue as to suggest a connection between the two. It is possible, although not demonstrated, that fatigue is partly due to an accumulation of xanthin products.

The *rigor* resembles that of rigor mortis in all respects: The muscle is hard, opaque, granular on miscroscopic examination, acid to litmus paper, etc.

This rigor may be produced in living animals by injection of sufficiently concentrated solutions, as also by chloroform and a few other substances.

All of these favor the clotting of muscle-extract. It will not do, however, to accept the latter as the explanation of the rigor, for many other substances produce clotting of the extracts with even greater readiness, but do not produce the rigor.

The effect of caffein upon smooth muscles consists in a stronger and more persistent contraction. Larger doses prolong the period of expansion.

The effect **upon cardiac** muscle is essentially the same as that upon skeletal muscle.

The heart muscle is, however, somewhat more resistant than the skeletal, for the heart of the frog is still found beating after the other muscles have gone into rigor.

With the frog's heart[1] (Fig. 50 *C*) *small doses* increase the absolute strength of contraction and the volume of blood thrown out in a given time. The duration of the systole is increased at the expense of the diastole. The rate is somewhat quickened, but this is soon replaced by slowing. The heart becomes permanently more and more contracted, finally reaches standstill, generally in systole, and then goes into rigor. The standstill is sometimes in diastole.

The analogy of these phenomena to those of skeletal muscle is most apparent.

(A) **Effect on the Mammalian Heart.**—*Small doses* cause an acceleration of rhythm; the strength of contraction and the relative duration of the phases being unaltered. The output of the ventricle is therefore increased. The quickening is not due to a paralysis of the vagus, for it occurs when the vagus has been completely paralyzed by atropin; nor is it due to a stimulation of the accelerator center, for it is seen after the excision of the stellate ganglia. It is further very improbable that it acts on the accelerator endings, for the details of the contraction curve differ from those produced by accelerator stimulation. Apocodein, which is said to paralyze the accelerator endings, does not prevent the quickening. This is also seen in the heart of the embryonic chick, before nerve fibers have become developed. The action must therefor be ***on the muscle substance*** itself, increasing its contractility. This is in agreement with the fact that the contractions are greater, if the rate is but little increased (Fig. 50 *B* and *C*).

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[1] Exercise 49.

Larger doses produce a further acceleration, through the same cause. This does not leave time for complete contractions, so that the excursions of the heart are diminished (Fig. 50 *A, b,* and *d*), and the output may be even less than with a normal heart, notwithstanding the increased rate. The relative length of the phases is also altered, the diastolic pause being usually shortened most.

Very large doses cause first a weakening of the cardiac muscle, so that the systole is shorter, then a slowing of both phases; or there may be ***auriculo-ventricular arythmia;*** the contractions, instead of arising in the auricles and descending to the apex, may have their origin in any part of the heart, so that the auricles and ventricles beat independently. This is a common result of over-stimulation of the cardiac muscle. It ends in fibrillary contractions and paralysis. The output of the heart is lessened by large doses. These changes result from an incipient rigor of the cardiac muscle.

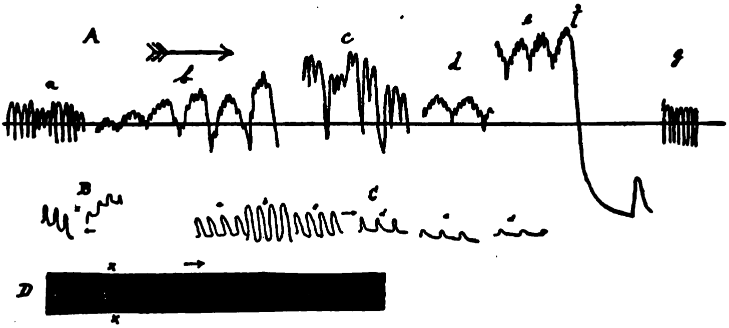

Fig. 50.—*Effects of Caffein:*
A. Blood-pressure tracing, dog; (a) normal; (b) after 20 mg. caffein per Kilo.; (c) to (g) after 70 mg. per Kg; at f, the vagus is stimulated electrically.
B: Myocardiogram, dog; caffein at ×.
C: Tracing from *frog's heart:* (a) normal; (b) to (d), increasing concentration of caffein. (The upstroke in *B* and *C* denotes systole.)
D: Respiratory tracing from unoperated rabbit. Caffein injected at ×.

(B) Effect on the Entire Circulation.—This differs, not only with the dose, but also with the somewhat variable interaction of the vasomotor, vagus, and cardiac effects. The typical results are shown in Fig. 50 A. Therapeutic doses (b) increase the rate of the heart, but lessen its force. The output may be somewhat increased, and this, with the stimulation of the vasomotor center, may cause a fair and sustained rise of blood-pressure, as shown in the tracing. However, this is very uncertain, since it is difficult to adjust the dose properly. This stage is also accompanied by palpitation.[1]

The larger respiratory variations in (b) are due to increased respiration.

With *larger doses* of caffein, the primary quickening is followed, in about half the cases, by a slowing (Fig. 50 *A c*), the caffein stimulating the vagus center. This stimulation soon passes off, as in (d). The pressure is at times fairly low, as in (d), at others high, as in (e). The quickening is not due to paralysis of the peripheral vagus mechanism, for electric stimulation (f) causes prompt stoppage of the heart.

The cerebral circulation shows marked constriction (Aliprandi, 1905).

(C) The Effect upon Metabolism.— Caffein causes a slight *rise of temperature,* partly by its action on the central nervous system, and especially by its direct muscular effects. In consequence of this, it also increases the metabolism — *i. e.,* the production of urea and CO_2. The older statements that it lessens metabolism are erroneous.

(D) The Effect upon the Kidneys.[2]— Under certain conditions caffein, and especially the other members of the series, may cause a considerable increase in the secretion of urine. In man, for instance, 0.5 Gm. of caffein increased the quantity of urine 42% above that secreted on the same allowance of water, but without the caffein (Raphael, 1894). The increase also involves the absolute quantity of urinary solids, but not in the same proportion, the concentration being diminished.

This diuretic action is peripheral, and does not depend upon changes of the general circulation. Its mechanism is not clearly understood, but it is commonly assumed to consist in a direct stimulation of the secretory epithelium. The caffein group differs from the peripheral diuretics in that it does not tend to produce renal irritation.

An older explanation referred the diuresis to increased blood-pressure. Von Schroeder (1886 and 1887) and Langgaard, however, showed independently that the effects on the urine and on the general blood-pressure bear no relation to each other. Indeed, the rise of pressure tends to interfere with the diuresis, since it depends mainly on vaso-constriction — a larger diuretic effect being obtained by counteracting the constriction by chloral, section of the renal nerves, or by using small doses, or theobromin, which acts to a lesser degree on the medullary centers. Caffein is also diuretic in excised kidneys, so that its action must be peripheral.

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[1] Palpitation is a purely sensory phenomenon, which may be caused either by an increased activity of the heart, as in this case, or by an increased excitability of the sensory nerves.

[2] Exercise 65.

Caffein causes an increase of the veinflow and of the volume in excised, artificially perfused kidneys, and the same phenomena occur commonly in the body. They imply a dilation of the renal arterioles, of peripheral origin, and consequently a higher filtration pressure. This is in line with the observations of Hellin and Spiro (1897) that caffein diuresis is prevented by the nephritic poisons which act on the glomeruli, and not by those which act on the tubules. It is not, however, the essential factor in the production of the diuresis, for the urine is commonly increased even when the peripheral dilator action is over-compensated by stimulation of the constrictor center (Phillips and Bradford, 1887).

The renal dilation is peripheral, since it occurs in excised kidneys. Loewi (1904) found the veinflow increased even when dilation of the kidney was prevented by incasing it in plaster of Paris. The caffein must therefor diminish the size of the renal cells. This has been demonstrated histologically by Von Sobieranski. Filehne (1902) showed that the absorbing power of renal cells is diminished during caffein diuresis. The increased bloodflow is therefor due to a lesser compression of the vessels by the smaller cells, rather than to a direct action on the arterial muscle. Von Sobieranski (1895) explained the diuretic action of caffein by the theory that it paralyzed the reabsorbing mechanism assumed by Ludwig's theory; but the experimental support of his view is inconclusive.

Anten (1901) found that the percentage of chlorids was lessened during caffein diuresis, whilst that of urea was unchanged. This may be interpreted in support of the view that caffein stimulates the secretion of urea apart from its action on the watery portion of the urine.

In starving rabbits, caffein breaks down the resistance to the excretion of chlorids; but it does not have this action in dogs, nor in man.

Dogs often fail to respond to caffein, but do so if the vagi are divided. Anten showed that this is due to an inhibitory effect of the vagus center on the renal cells.

The absence of irritation in caffein or theobromin diuresis is shown by the observations of Emerson (1902) and of Sollmann and McComb (1898) that the percentage of albumin is not increased, and that, therefore, no injury was caused in these cases. Their only danger would lie in the increased work which they put on the kidney. (Theophyllin, however, does not seem to be free from irritation — Pouchet and Chevalier, 1903.) On the other hand, the usefulness of these drugs is lessened by the fact that they cannot act if the renal elements are greatly changed and their action does not seem to be sustained well on continuous administration (Le Noir and Camus, 1903).

Caffein, so far as known, has no effect on *other gland cells,* nor upon *muscle-nerve endings,* nor upon *ganglia.*

Caffein causes a peculiar vacuolization and condensation in the protoplasm of the ameba and other infusoria, due probably to its basic nature.

Small doses increase the movement of *leucocytes* in shed blood, whilst large doses kill them. It has *no effect* on the red corpuscles, nor on fibrin formation.

IV. ABSORPTION, FATE, EXCRETION.

Caffein is rapidly absorbed. In its passage through the body it undergoes change, only a small part being excreted unaltered (8 to 21% of caffein, 32% of theobromin).

The change consists largely in the loss of methyl groups, the caffein (tri-methyl-xanthin) being converted into di- and mono-methyl-xanthins. Only 30% to 40% are excreted in this way. On account of the similar composition one might be tempted to suppose that the rest of the caffein is converted into uric acid. This is, however, not the case, the oxidation being more complete and probably reaching urea. Of the other members of the series, theobromin suffers a similar fate, but a larger percentage is excreted unchanged. The greater part leaves as heteroxanthin. Hypoxanthin and xanthin are excreted largely as uric acid.

V. DIFFERENCES IN THE MEMBERS OF THE GROUP.

Caffein has the *strongest action on the central nervous system*. Paraxanthin is the *most diuretic* member of the group, then comes theophyllin (theocin), then theobromin, and lastly caffein. The mono-methyl-xanthins are also diuretic. The *action on the muscle* is parallel to the diuresis. Purin causes a central stimulation, followed by paralysis. Its action on muscle is weak. Xanthin also has only a very weak diuretic action. Uric acid does not share the characters of the group.

VI. TOXICOLOGY.

The toxicology of caffein is unimportant. The *symptoms* produced by large, but not fatal, doses have been sufficiently discussed; those arising from the *central nervous system* are: excitement, increased reflex irritability, tremors, etc. These predominate, and are associated with *palpitation* and quickened, irregular pulse.

Fatal doses — very rare in man[1] — show tetanus, coma, and death, usually by paralysis of the heart. There are no post-mortem lesions.

The *treatment* would consist in evacuation, and bromids or other narcotics. The usual chemic antidotes are of little value, with the possible exception of permanganate.

VII. THERAPEUTICS.

(*A*) *The Effects upon the Spinal Centers.*— These are not much utilized, since the same effects are obtained by strychnin in a better and purer form. Strychnin avoids especially the action upon the brain (wakefulness) and heart (palpitation).

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[1] A fatal case of poisoning from 0.6 Gm. is reported by Allard, 1904.

(*B*) *The Effect upon the Medullary Centers.*— Here, also, strychnin is preferred in almost all cases where it is at hand, for doses of caffein large enough to affect the medulla are apt to have the above side-effects.

In cases of *narcotic poisoning,* where strychnin is often not at hand, and especially in morphin and alcohol poisoning, where it is wished to stimulate the brain as well, this drug is very useful. Caffein forms a useful addition to drugs, such as the *antipyrin* series, in which depression of the central nervous system is an undesired side-action.

It may also be of great service in certain cases of *asthma.*

The use of caffein in *migraine* is entirely empirical, since the nature of this disease is not known. It is undoubtedly useful, especially in the combination known as migrainin.[1] It is also used in trigeminal neuralgia, and often gives relief. It is possible that these actions are due to the effect on the higher centers. Caffein may be similarly useful in *nervous dyspepsias.*

(*C*) *Its effects on the brain* are the most important, but can be better discussed under its habitual use.

(*D*) *Effect upon the Kidneys.*— The diuretic effect of the caffein group is utilized when the secretion of urine is deficient, or for the removal of fluid or of toxic substances from the body. It is especially useful in nephritic or cardiac effusions. When used in cardiac disease, it should be combined with digitalis. In certain cases, the caffein diuretics are not effective; nor is the effect very lasting, even when the doses are repeated. To avoid the interference of vaso-constriction, the dose of the citrated caffein should not exceed 0.5 Gm. The addition of chloral increases its efficiency. The theobromin compounds — diuretin or agurin — are more certain. The most effective dose of these is 2 to 3 Gm. Theocin is still in the experimental stage.

(*E*) *Effect upon the Heart.*— Caffein has been used considerably in heart disease, especially in stenosis and mitral insufficiency. Neither clinical observation nor pharmacologic experiments have assigned to it so prominent a place as to digitalis, and it may well be discontinued for this purpose.

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[1] Caffein, 9; antipyrin, 85; citric acid, 6. Used in doses of about 0.6 Gm. (10 grains); or the Pulv. Acetanilidi Comp.

VIII. CAFFEIN BEVERAGES.

Coffee and tea are used principally as beverages, and to relieve psychical and physical fatigue. They may in some cases be substituted for caffein in therapeutics, although their effects are not quite identical with those of the alkaloid. The differences are due to the other constituents.

Tea contains considerable *tannin,* probably identical with that of oak bark. It is therefore astringent, checks diarrhea, and large doses interfere with digestion — by precipitating proteids and albumoses; by lessening absorption; and by irritating the gastric mucosa. With smaller doses, however, the degree of irritation may even be beneficial. The tannin is extracted rather slowly, so that tea which has been boiled or infused for a long time is particularly detrimental.— Tea further contains *volatile oils,* which give it the perfume. These add greatly to its acceptable taste. They are stimulant to the brain, reinforcing the central actions of caffein. The green tea is richer in oil than the black variety.— The effects of the *hot water* are also important; this acts as a reflex stimulant, and as a diuretic and diaphoretic.

Coffee contains a *tannin* (in even greater amount than tea); but this differs very much in its chemic and pharmacologic properties from the tea-tannin: it does not precipitate proteids, and is but slightly astringent. It is therefor less harmful to digestion. (The caffein itself has no effect on digestion.) The beverage is, however, even more detrimental than tea in some cases of dyspepsia. This is due to the *caffeol,* the empyreumatic oil formed in the roasting of coffee. This substance is a mixture, containing about 50% of furfurol alcohol, and small quantities of valerianic acid, phenols, and other unknown products. The aroma is due to a nitrogenous ingredient. The oil is a local irritant, which accounts for digestive disturbance. It also gives to coffee a slight laxative action. The central actions resemble those of caffein and of the essential oil of tea.

The caffein-free distillate from infusions of tea or roasted coffee causes an increase in the rate of respiration, and a psychic and muscular restlessness. The pulse is not altered. However, some experimenters have failed to find any action on respiration. Large doses of the caffeol give rise to paralytic phenomena.

The *differences between the caffein beverages and the alkaloid* consist therefore in a greater psychic and respiratory stimulation (by the oil); a greater diuretic action (from the water); a comparatively lesser action on the heart and muscles; a tendency to derange digestion (by the caffeol or tea-tannin); and a laxative action with coffee. The reflex stimulant effects of the *hot water* also contribute to the action.

As to the **differences between coffee and tea:** The psychic effects are greatest with green tea or well roasted coffee. Strong tea, especially if infused for some time, is more detrimental to digestion, is astringent, and checks peristalsis. Either beverage is generally contraindicated in gastritis; sometimes the one, sometimes the other, is better borne. It is popularly believed that coffee injures the complexion. This could occur through its action on digestion. As a chemic antidote in alkaloidal poisoning, coffee is less efficient than tea (see p. 89).

The *habitual use of caffein beverages* depends upon the pleasant sensations which accompany the stimulation. Caffein *in moderate doses does not seem to become noxious with habitual use.* When the amount taken is too large, it presents the same symptoms in persistent form which are seen in acute poisoning: tremors, nervousness, palpitation, etc. The mind also seems to suffer, and *chronic melancholia* is a frequent phenomenon.

The excessive use of these beverages is apt to do most harm by their disturbing digestion.

The use of coffee arose in Arabia and Egypt about 1450. Coffee and tea were introduced into Europe about the last quarter of the seventeenth century, a period which was characterized by the common introduction of many new products, such as the potato, cinchona, tobacco, and chocolate.

Whilst the consumption of the caffein beverages is ordinarily a mere luxury, pleasant but otherwise useless, it may have a distinct value in special conditions.

The principal benefit derived from these beverages is a *diminution of fatigue,* mental and muscular. The action on *mental fatigue* is accounted for by the stimulation of the psychic areas, an action greatly enhanced by the volatile by-products. For this purpose one should, therefore, employ well-roasted coffee or green tea with short infusion. These would also be especially active in producing wakefulness.

The effect upon the *muscular fatigue* may be explained both by easier transmission of reflexes (a given stimulus reaching the muscle more readily) and by increased contractility and excitability of the muscle-fibers themselves.

This action has been demonstrated beyond a doubt; *e. g.,* soldiers can endure more severe marches when given coffee. It can also be demonstrated with the ergograph. It will occur only if the amount of energy-yielding substance in the muscle has not been exhausted, and will not have any effect after fasting. Sugar is then the most efficient means for the relief of fatigue. The effect of caffein is never very prolonged, but is not followed by depression.

Coffee is sometimes used against *hunger*. It acts only by covering up the condition through the exhilaration which it produces, and cannot be of any real benefit. On the contrary, the metabolism is increased.

Cocoa and chocolate are also used as mild stimulants, their effects being less pronounced than with the others. On account of the large amount of fatty matter which they contain, they are to some extent nutritious, although this fat is not very digestible.

Coffee and chocolate are also used to cover up the taste of medicines; *e. g.*, iron, quinin, bitter substances, castor oil, cod-liver oil, etc.

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The crude drugs of this family are mainly articles of consumption, and are not official, with the exception of Guarana. The National Formulary gives directions for the preparation of fluidextracts of coffee, tea, and kola, and for syrup of coffee. These are used mainly for flavoring. All the preparations are miscible with water or alcohol.

* **Caffea.**—*Coffee.*— Seed of *Coffea Arabica,* Rubiaceæ.[1] Native of Arabia and Abyssinia, cultivated in all tropical countries.

Caffein, 1 to 1.3%; caffeotannic acid, 6 to 34%.

The leaves also contain caffein, and are used by the natives in the same manner as tea.

In the process of roasting, a very small amount of caffein is lost (depending upon the degree of heat used), and empyreumatic oils ("caffeol"), of unknown composition, are produced.

An ordinary cup of coffee contains 0.1 to 0.2 Gm. of caffein.

* **Thea.**— *Tea.*— Leaves of *Camellia Thea,* Ternstrœmiaceæ. Southeastern Asia, cultivated. (Also capable of cultivation in the United States.)

Caffein, 1.5 to 4%; volatile oil; tannin, 5 to 15%.

An ordinary cup of tea contains 0.1 to 0.2 Gm. caffein.

The black and green teas differ only in the treatment to which the leaves are subjected (a fermentation with the black variety).

* **Kola.**— *Cola.*— Seed of *Cola acuminata,* Sterculiaceæ. Tropical western Africa and cultivated in West Indies.

Caffein, 2%; a little theobromin formed from glucosid in drying; volatile oil; tannin.

Often roasted. Used by the natives as masticatory and to render bad water palatable. Valued so highly as to be used as money.

Guarana.— *Guarana* (Brazilian Cocoa).— A dried paste, prepared by the Indians, consisting chiefly of the roasted and pounded seeds of *Paullinia Cupana,* Sapindaceæ, northern and western Brazil.

Caffein, 4 to 5% (at least 3.5%, U. S. P.); tannin, gums, resin, volatile oil.

Fluidextractum Guaranæ: 3.5% of alkaloids. *Dose:* 1 to 4 c.c. (¼ to 1 drachm) (2 c.c. = 30 ♏, U. S. P.).

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[1] The same order yields cinchona, catechu, and ipecac.

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* Not official.

* **Mate.**—*Paraguay Tea.*—The leaves of *Ilex paraguayensis,* Ilicineæ. Brazil and Argentine.

The commercial leaves are slightly torrefied.

Caffein, 0.2 to 1.6%; tannin, 10 to 16%; a little volatile oil.

Used in making a beverage.

Other species of Ilex probably also contain caffein, and some of those growing in the Southern States are used as *Apache tea.*

* **Theobroma.**—*Cacao* (not to be confused with Coca[1]).—The fermented, dried, and often roasted, seeds of *Theobroma Cacao,* Sterculiaceæ. Tropical America, cultivated.

Theobromin, 1.5 to 4.5%; trace caffein; fat, 50%; starch, 10%; tannin.

The theobromin does not exist in the fresh seed, but is derived from a glucosid during the process of preparation. In the powdered cacaos of commerce, part of the oil has been removed, so that only about 25% remains.

Chocolate consists of melted cacao and sugar in various proportions, often with the addition of flavors or starch.

Caffeina, U. S. P., B. P.—$C_8H_{10}N_4O_2 + H_2O$, Tri-methyl-xanthin, prepared from any of the above plants. The free base is soluble in 45.6 water; 53.2 alcohol. *Dose:* 0.06 to 0.25 Gm. (1 to 4 grs.) (0.065 Gm. = 1 grain, U. S. P.).

Preparations:

C. Citrata, U. S. P. (Caffeinæ Citras, B. P.) (not a true salt, but a mixture containing 50% each of caffein and citric acid).—Soluble in 25 water. *Dose:* 0.15 to 0.5 Gm. (2 to 8 grs.) (0.125 Gm. = 2 grs., U. S. P.).

C. Citrata Effervescens, U. S. P., B. P. = 2% of caffein. *Dose:* 4 to 15 Gm. (1 to 4 drachms) (4 Gm. = 1ʒ, U. S. P.).

* *C. Sodio-benzoas,* N. F.
* *C. Sodio-salicylas,* N. F. } = 50% caffein; soluble in 2 parts water.

Elixir Caffeinæ, N. F.—1.75%. 4 c. c. (1 drachm) = 0.06 Gm. caffein (acidulated).

Pulvis Acetanilidi Comp., U. S. P., contains 10% of caffein (see Index).

Theobromina, $C_7H_8N_4O$.—The alkaloid of Theobroma Cacao. On account of its comparative insolubility (1,700 parts of water), the free alkaloid is but rarely used. The solubility can be greatly increased by combining it with an alkali. These compounds are, however, very caustic. The corrosive action is greatly reduced by the addition of salts, without lessening the solubility. Such mixtures of sodium-theobromin with equimolecular quantities of salts are the form in which theobromin is used in therapeutics. They are readily decomposed by acids, so that they must not be exposed to the air (to exclude CO_2), nor should they be given at meal time (to avoid the HCl). The *dose* is 1.5 to 3 Gms. (20 to 45 grains), in Aqua Menthæ Piperitæ. They are probably too caustic to be used hypodermically. The older preparation is **Theobrominæ Sodio-Salicylas** (*Diuretin*). It contains 50% of the alkaloid. The **Theobrominæ Sodio-Acetas** (*Agurin*) is still less caustic, avoids the salicylate action, and contains 63.3% of alkaloid. Both are very soluble in warm water.

Theophyllin is found on the market under the name of *Theocin.* It is a more efficient diuretic, but it is doubtful whether this advantage offsets the greater cost and other disadvantages. It is difficultly soluble; *dose,* 0.2 to 0.3 Gm. (3 to 5 grains).

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[1] Cacao = Theobroma Cacao.
Cocoa = A palm yielding cocoa nut.
Coca = Erythcoxylon Coca, yielding cocain.

(C) PICROTOXIN GROUP.

This comprises a number of bodies closely related by their pharmacologic action, and probably also by their chemic composition. Of the latter little is known. They belong to a group of non-alkaloidal, non-nitrogenous vegetable substances, more soluble in alcohol than in water, sometimes called "active resinoids." Some of them are glucosids. The group has at present very little therapeutic but some toxologic interest.

I. MEMBERS.

Picrotoxin, the active constituent of Cocculus indicus, is the principal member of the group; it splits readily into picrotoxinin, having the same action, and into the inactive picrotin. Other principles belonging to this group are: *Cicutoxin,* from Cicuta virosa — water hemlock. *Œnanthotoxin,* from Œnanthe crocata. *Coriamyrtin,* from Coriaria myrtifolia. *Digitaliresin* — decomposition product of digitalin and digitalein. *Toxiresin* — decomposition product of digitoxin. *Oleandresin* — decomposition product of oleandrin. *Phytolaccotoxin,* mainly from Phytolacca Japonica. A similar principle exists perhaps in pokeroot (*Phytolacca decandra*); but this has not been demonstrated.

II. SUMMARY OF ACTIONS.

1. Stimulation, followed by paralysis, of the medullary centers.
2. Some stimulation of the spinal cord.

III. DETAILS OF ACTION.

The effect upon the *medulla:* The principal symptom of picrotoxin poisoning consists in *convulsions* of the type characteristic of a stimulation of the medulla. They are, indeed, situated in the medullary convulsion-center, since they are not affected by excision of the cerebrum, but practically disappear after destruction of the medulla.[1]

This is especially the case in mammals. In the frog, strychnin-like spasms of spinal origin often appear shortly after the medulla is destroyed, which were before masked by the more intense stimulation of higher centers.

The convulsions are not so much dependent upon reflex stimulation, so that they are probably in part due to a direct stimulation.

Respiratory center: The respiration is accelerated before the convulsions. Later it becomes fixed in the spasm, and in the following collapse may be slowed. Asphyxia may, therefore, occur.

Spasms of the laryngeal muscles leads, with the frog, to distention of the body with air and to a characteristic cry similar to that sometimes heard with strychnin. With digitaliresin, toxiresin, and oleandresin, the convulsions are preceded by immobility.

Vasomotor center: There is a general rise of blood pressure, notwithstanding the slowed pulse, and independent of the convulsions, showing a stimulation of the center.

Vagus center: The heart is greatly slowed, and may even cease for a time. After division of the vagi the heart will return almost to normal. There is, however, some depression of the cardiac muscle involved in this slowing. Later there may be a quickening, partly due to stimulation of the accelerator center and partly to paralysis of the vagus center and to fatigue of its endings.

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[1] Exercise 38. See page 146.

The *vomiting, salivary,* and *sweating centers* are also excited. The sweat may, however, be suppressed by vasomotor constriction. The emetic effect is used therapeutically in the case of phytolacca.

Spinal cord: As has been seen, a stimulation of this structure is shown, under suitable conditions, by increased reflex irritability. The centers of defecation and urination may also be excited. Uterine spasms have also been observed as dependent on stimulation of the spinal cord, since they cease upon destruction of this organ.

With larger doses, all the stimulant effects give way to paralysis.

IV. TOXICOLOGY.

Poisoning with the common plant Phytolacca (poke-berries) is not rare. The Cocculus indicus (fish-berries) have been used for poisoning fish (in whom it also produces medullary stimulation and paralysis), and this meat is highly toxic. It has also been used to give a bitter taste to beer, which thus becomes poisonous. 2.4 Gm. of the berries (0.015 to 0.025 Gm. of picrotoxin) are fatal. The toxic effect sometimes seen on administering old infusions of digitalis may also be due to members of this series. More direct work on this would be desirable.

Several cases of *criminal picrotoxin poisoning* (used as "knockout drops") have occurred recently. The poison disappears rapidly during putrefaction (within one or two weeks); so that the *toxicologic analysis* must be made promptly. The characteristic effect of the isolated poison on the frog constitutes the best test. The intensely bitter taste (discernible in dilutions of 1 : 80,000) may arouse suspicion.

The *symptoms* of poisoning consist in: vomiting, salivation, acceleration of respiration, slowing of pulse and palpitation of heart. These are rapidly followed by stupor and unconsciousness. In ½ to 3 hours this again is succeeded by convulsions, which may be repeated several times. Death occurs by asphyxia.

Treatment.—The chemic alkaloidal precipitants would not be efficient. The best treatment would be emetics (if vomiting has not occurred), permanganate, chloral, and chloroform. The combined administration of chloral, morphin, and minimal doses of atropin has recently been recommended as the result of animal experiments.

V. THERAPEUTICS.

The medullary stimulation produced by this group would be highly important if we could find members which were quickly and certainly absorbed. This has not been accomplished so far, the action being uncertain and difficult to control. Coriamyrtin holds forth some promise, but has not been sufficiently tried. The indications for their use would be the same as those for strychnin (medullary effect). Phytolacca has been used as an emetic, but its action is uncertain and is apt to be followed by dangerous effects. Picrotoxin is used externally against pediculi; internally, against the night-sweats of phthisis, and in epilepsy, where its benefits are, however, doubtful.

MATERIA MEDICA.

* **Cocculus indicus.**—*Fish-berries.*—The seeds of *Anamirta paniculata,* Menispermaceæ. East India.
Picrotoxin (1 to 1.5 %), inactive alkaloid, resin, fat.
Dose: 0.1 to 0.2 Gm. (1½ to 3 grs.).
(Decoction used externally for killing vermin.)

Picrotoxinum (B. P.).—*Picrotoxin.*—Neutral principle.
Soluble in 9 alcohol, 240 water.
Dose: 0.0005 to 0.002 Gm. ($^1/_{120}$ to $^1/_{30}$ grain).
Action uncertain.

* **Cicuta virosa.**—*Water Hemlock.* Europe.
Cicuta maculata and bulbifera. United States.
Umbelliferæ. Of some toxicologic interest.[1]

* **Phytolaccæ Fructus.**—*Poke-berry.*—The fruit of *Phytolacca decandra,* Phytolaccaceæ. North America.
Irritant principles, gum, coloring-matter.

Phytolacca (U. S. P.).—The root of the above.
Constituents as above; also tannin and oils.
Average Dose (U. S. P.): Emetic, 1 Gm. (15 gr.); Alterative, 0.125 Gm. (2 gr.).
Fluidextractum Phytolaccæ (U. S. P.): *Dose:* as the drug.

Poke-root and berries are used popularly as emetics, cathartics, and "alteratives." The active principles are not known. The young sprouts, collected in early spring, seem to be innocuous, as they are boiled and eaten like spinach.

(D) SUMMARIES OF CONVULSANT SERIES.

1. Drugs Stimulating the Vasomotor Center.—*A rise of blood pressure may be brought about* by a quickening of the heart, by an increase of the volume of blood thrown out at each contraction, or by a *contraction of the vessels.*

The latter may be effected *peripherally,* either through direct action on the muscles or the endings, or it may be effected through the vasomotor *center.*

The vasomotor center may be stimulated:

1. Reflexly, through stimulation of the sensory nerves.

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[1] Description and illustrations of the poisonous plants of the United States are given in Bulletin 20, prepared by Mr. V. K. Chesnut, and issued by the Division of Botany, U. S. Department of Agriculture (1898).

* Not official.

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2. Directly, through accumulation of CO_2 in the blood.

3. *Directly, through the action of drugs.*

The latter alone will be considered in this place. The following drugs stimulate the vasomotor center directly:

Strychnin: the action is rapid and free from side-effects, but it is doubtful whether small doses are very efficient. Excessive doses cause paralysis of the vasomotor center.

Caffein: large doses are required and such as will produce headache, wakefulness, and perhaps palpitation.

Picrotoxin Group: the action of this is confined to the medulla, and would for that reason be the most desirable; however, the action develops slowly and is difficult to control.

Digitalis Group: the vasomotor action is overshadowed by a simultaneous stimulation of the cardiac muscle, which is, however, usually desirable. The effect is developed rather slowly — in half an hour.

Groups of Atropin, Aconite, Nicotin, Ergot, and Ammonia: the effect is small, uncertain, and obscured by side-actions.

A stimulation of the vasomotor center will be *useful* by producing a rise of the blood pressure. The benefit will be only temporary if the heart-muscle is weakened, since the rise is produced at the expense of the heart; *i. e.*, by increasing its work. The benefit is *more permanent when the center is depressed,* as in shock, narcotics, or in partial paralysis of the center.

The direct stimulation of the center by drugs (strychnin) has the *advantage over reflex stimulation* in that it can be maintained continuously for a much longer time. Reflex stimulation is more useful when a short but quick stimulation is desired.

2. Respiratory Stimulants: *i. e.*, those conditions which quicken or deepen the respiration through a stimulation of the respiratory center.

This stimulation may be:

1. Reflex, from stimulation of peripheral nerves.

2. Direct, through an increase in temperature or venosity of the blood.

3. Direct, through drugs.

Drugs stimulating the respiratory center directly:

Strychnin has a quick and powerful action, practically free from undesired side-effects, but the effect is *not lasting.*

Caffein acts more slowly, but is more lasting; it produces wakefulness, etc.

Atropin: the effect is not so very great, but since it also paralyzes the bronchial muscles and dries the bronchial secretion, it is especially indicated in *asthmatic conditions.*

With the groups of *picrotoxin, HCN, and* NH_4, the action is uncertain and impure.

Indication for these remedies is lowered activity of the respiratory center, such as may occur in exhausting diseases; fatigue, as in asthma; or in depression by drugs (narcotics).

3. Convulsants.— As far as these have toxicologic importance:

Convulsions may be produced by asphyxia or through direct stimulation of the convulsion centers.

Asphyxial convulsions can be removed by artificial respiration. They occur in the course of poisoning by many drugs which depress the respiratory center or interfere mechanically with the admission of air into the alveoli. To the former belong chloroform and anesthetics; to the latter, CO, CO_2, and N_2O.

Drugs may stimulate the center either in:

Motor areas, Pons, Medulla.	The convulsions are epileptiform or choreiform; if tonic, there is emprosthotonos.
Spinal cord:	The convulsions are tetanic; opisthotonos.

Usually the seat of the convulsion is more or less widely spread, and there is perhaps no drug which affects exclusively one of these centers.

Spinal convulsions are produced most typically by strychnin and caffein; *Medullary Convulsions* by the picrotoxin group; cornutin (from ergot); camphor; carbolic acid; ammonia; veratrin. *Cerebral Convulsions* are seen with cannabis indica and absinthe.

4. Shock or Collapse.— Shock or collapse may be defined as a sudden depression of the activity of the medullary center. If this depression results from a reflex, it is called shock; if produced directly, collapse. Shock is ordinarily produced by traumatism; it consists probably in a reflex inhibition.

Some authors reserve the term "shock" for the more severe grades of depression, applying "collapse" to the lighter grades, regardless of whether the effect is direct or indirect. The first definition appears more useful.

Collapse may be produced by anemia, asphyxia, or drugs. In any case there is an involvement of the vasomotor and respiratory centers, also of the cardiac (vagus) center; but the latter is of very little practical importance. The vasomotor paralysis is the gravest source of danger.

Depression of the heart may be the cause of the anemia.

Drugs causing collapse:

I. Indirectly:

1. All which stop the heart.
2. All those which interfere mechanically with respiration.

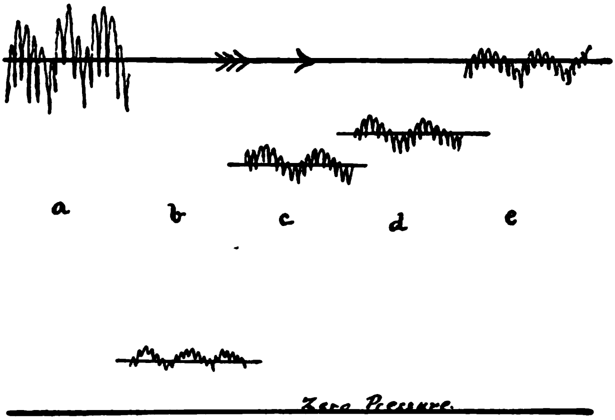

Fig. 51.—*Effect of Hemorrhage and Saline Injection:* Carotid pressure, dog. (a) Normal tracing; (b) just after completing the hemorrhage; (c) just after completing the intra-venous saline injection; (d) and (e) are taken later, and show the further recovery.

3. Those which produce a violent reflex irritation (caustics). This is really "shock."

II. Directly: i. e., those in which the collapse is not preceded by other conspicuous symptoms:

Cocain, Physostigmin, Benzol derivatives (aromatic series), Hydrocarbon narcotics.

Treatment of Collapse and Shock.—The treatment of these conditions should be directed to removing the cause, if possible; and to meeting the symptoms. As regards the *symptomatic treatment,* the *respiration* should always receive attention. Strychnin, caffein or atropin, hypodermic or rectal injections of camphor, and artificial respiration are used according to the requirements of the case. These may suffice in light cases; but in severe shock the *vasomotor depression* requires the greatest attention. The same direct and reflex stimulant measures which are used to improve the respiration also react favorably on the circulation; but they do not suffice in severe cases, since the depressed vasomotor center reacts very sluggishly or not at all. Every effort must be made to maintain an efficient blood-pressure in the medullary and coronary circulation. This can be done by *forcing all available blood toward the head,* by lowering the head of the patient or by tightly bandaging the extremities. Crile employs a pneumatic suit for this purpose. This is inflated, producing any desired degree of compression. The intravenous injection of suprarenal alkaloid is also effective, even when the vasomotor center is completely paralyzed, but more experiments are needed before its use on patients can be endorsed.

The intravenous, intraperitoneal or hypodermic injection of 300 to 1,000 c. c. of *normal saline solution* (0.9% NaCl), of a temperature of 40 to 45° C. (104 to 113° F.), produces respiratory and vasomotor stimulation, mainly by increasing the mass of circulating fluid. The effect is of distinct temporary benefit, but is not lasting in ordinary shock or collapse. The effect can be somewhat improved by using 0.5% of sodium bicarbonate in 0.8% NaCl (Dawson, 1905). In normal animals, the rise of blood pressure is very small. However, in the form of collapse produced by severe *hemorrhage,* saline injection has an excellent and persistent effect (Fig. 51). *Cooling* should be prevented by the application of heat.

CHAPTER IX.

ALKALOIDAL HYPNOTICS.

(A) MORPHIN GROUP.

I. MEMBERS.

The members are mainly the various opium alkaloids: Morphin, codein, narcotin, papaverin; also the esters obtained by replacing one or two H atoms in morphin by radicles: Heroin (= diacetyl morphin); Dionin (= ethylmorphin); Peronin (= benzylmorphin).[1]

II. SUMMARY OF ACTIONS.

1. Simultaneous stimulation and depression of different parts of the central nervous system.
2. A local action on the peristaltic mechanism of the intestine.
3. In large doses, a paralysis of the heart muscle.

(There is no effect upon the peripheral sensory nerves.)

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[1] Codein is a natural substitution product of the same type, i. e. methyl morphin.

1. Central Nervous System.[1]— **(A) The Brain.**—(*a*) In the *frog* the development of the symptoms corresponds exactly to progressive removal of the brain. They can be well made out if the poisoning is slow. The depression begins with the *hemispheres*. There is a diminution, and then absence, of spontaneous movements; but when aroused, the animal will act quite normally. It sits in the normal position, shows the croaking reflex, and will climb up an inclined plane. When placed in a tumbler filled with water and inverted in a large vessel of water, it will at first leave the glass, but later on it will not do so. At this time it will not avoid obstacles in jumping. The lower brain is next involved, this being shown in an *incoordination* of movements. When placed on its back, the animal will make efforts to turn, without being able to do so. Later it will lie quiet. The *spinal cord* is then involved and the reflexes are lessened.

After the animal has remained in this depressed condition for a variable time a *secondary tetanus* sets in. This is of the strychnin type. It usually passes into complete *paralysis*. The heart is still beating at this stage.

(*b*) In *mammals* the course is similar, although there is not such an isolation of the symptoms, both because the centers are more intimately correlated and because the action is more rapid. The secondary tetanus is less prominent, but in small animals quite manifest. A stimulation of various higher centers of the nervous system, simultaneous with the depression of others, is much more conspicuous than in the frog.

One or the other of these two sets of actions, stimulation or depression, may predominate in different animals or in different individuals of the same species. On account of these individual differences, the symptoms are not uniform, and it is impossible to pronounce on one type of morphin-poisoning. Each part of the central nervous system requires separate study.

Hemispheres.— In mammals the *first effect*, produced by doses too small to elicit any other symptoms, is *diminished sensibility to lasting impressions*. Especially stimuli giving rise to *pain, cough,* and other disagreeable sensations, are much diminished in their effects. With somewhat larger doses other persistent external impressions, such as those produced by light, sound, etc., are also weakened. The *sensibility to sudden stimuli is diminished but not abolished.* It seems to be the *attention* which suffers mainly. The impressions reach the brain, but produce little effect there, and, attracting little attention on the part of the animal, are neglected. The faculty of memorizing also suffers severely (Weygandt, 1903). These conditions exist in practically all animals possessed of a higher brain.

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[1] Exercises 40 and 41.

In *larger doses* morphin affects other portions of the hemispheres besides those having to do with external impressions, and the effects upon these are variable. Its typical effect in man is to produce *quietness,* which, aided by suppression of external stimuli, passess into a dreamy, abstracted condition, or into torpor, *sleep,* and coma, according to the dose.

The milder degrees of narcosis[1] are mainly due to the blunting of the attention — to the exclusion of external stimuli — and not to depression of the entire cerebrum. This is indicated by the fact that the sleep produced by small doses is refreshing, and the patient can be readily and completely awakened. Other facts point to the same conclusion. The sleep or coma produced by *large doses,* however, involves a more extensive depression; in the deeper degrees of narcosis it may be impossible to arouse the patient to complete consciousness.

This narcosis is *not seen in all animals.* It is the usual effect in *man,* in the *dog,* rabbit, guinea pig, white rat, mouse and sparrow. In the *cat,* horse, ass, beef, sheep, pig and goat, on the other hand, morphin in moderate doses produces almost pure *excitement,* manifested by restlessness and incessant movement.

But even in this condition one may notice the depressing action upon the attention, for the animal does not avoid obstacles in a normal manner, and when it comes into violent contact with some object, this does not seem to make any lasting impression upon it, and does not teach it to be more careful.

Some Eastern races, especially the Malays, as well as some individuals of other races, most frequently women, also manifest almost pure excitement effects, so that the morphin produces wakefulness instead of drowsiness. In many cases this restlessness seem to precede the narcotic action, although not the lowering of the attention. Dogs commonly show marked excitement before the depression sets in.

The *other members of the group,* especially codein and heroin, show a comparatively slight quieting, and comparatively strong excitant, action. With these, the maximum of hypnosis is soon reached, and if the dose be raised beyond this point, the slight depressant action disappears entirely and is replaced by excitement. These phenomena seem analogous to the secondary tetanus. Different animals show the same differences with regard to the narcotic and stimulating actions of these derivatives as they do with morphin.

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[1] *Narcotics* are substances having the property of stupefying. The following drugs are classed under this heading: Aconite, hydrocarbons, belladonna, cannabis, conium, digitalis, humulus, hyoscyamus, lactucarium, opium and stramonium.

Morphin is by far the most active member of this series, as far as the hypnotic and analgesic effects are concerned.

The *motor areas* may be very differently affected. In dogs one sees very frequently a paralysis of the hind legs, resulting in a crouching (hyenoid) walk, which probably has its cause in depression of the cerebral center. These animals always show a clumsiness in their voluntary movements, bearing the closest resemblance to that produced by ablation of the motor areas. Heroin gives the same effects.

On the other hand, one often sees epileptiform convulsions, tremors, or choreiform twitchings of single limbs which seem to arise from irritation of this center. The excitability of the motor areas to electric stimulation is not affected.

On the *special senses* morphin seems to have no effect. The changes which are noted — namely, a less acute perception — can be accounted for entirely by disturbance in the attention. On the other hand, the reflexes to which they give rise when suddenly excited, are increased. This depends upon the *heightened excitability of the spinal cord.*

The *imagination* is peculiarly affected. In most people the period of abstraction and light sleep is filled with dreams which are usually pleasant.

At least the greater part of this may be ascribed to the suppression of the external, and especially of unpleasant, impressions. Whether there is also a stimulation of an "imagination center" must be left undecided. Perhaps the *aphrodisiac effects* can be explained by this unrestrained imagination, perhaps also by stimulation of the center in the cord, for the more stimulating members of the group, such as heroin, produce erection in dogs. In man, on the other hand, heroin is said to act as an anaphrodisiac.

(**B**) **The Medulla.**— The effects upon the medulla are very characteristic. There is less variation in individuals, but the separate centers show a very different reaction.

(*a*) *The Respiratory Center.*— Morphin depresses this center. The respiration is rendered slower and more shallow by *small doses,* and the volume of air respired in a given time is diminished.[1] The CO_2 of the blood therefore rises, although less oxygen is consumed on account of the quieting influence of the morphin. The sensitiveness of the center to reflex stimulation (such as gives rise to cough) is also greatly diminished. *Larger doses* cause further depression, the respiration becoming very slow, shallow and irregular, and often assuming the intermittent, Cheyne-Stokes type.

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[1] In the dog, the primary slowing of the respiration is almost invariably followed by a sudden large increase (the rate may rise in ten minutes from 24 to 234.) This is again succeeded by slowing.

The phenomenon of **Cheyne-Stokes respiration** consists in an alternation of short periods of efficient respiration with long periods during which the respiration is very slow and feeble. The periods shade into each other gradually (see Fig. 52).

Cheyne-Stokes respiration is produced by a large number of drugs which have in common a depression of the respiratory center.

The inefficient respiration leads to *asphyxia,* with the effects described on page 147. The asphyxial convulsions are often absent, especially in man, on account of the depression of the central nervous system. The asphyxia constitutes the usual cause of death.

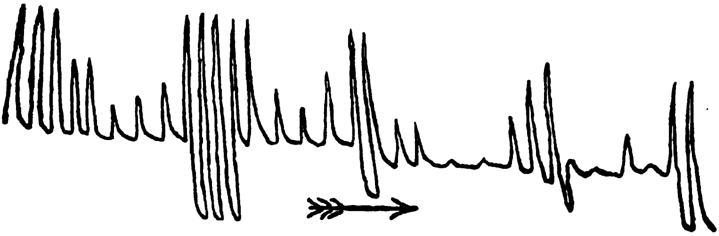

Fig. 52.— Cheyne-Stokes Respiration (HCN poisoning, dog).

The action of *Heroin on the respiration* differs somewhat from that of morphin. This drug also depresses the sensitiveness of the respiratory center, but much more to reflex stimulation (cough) than to direct stimulation (venosity of the blood). *Therapeutic doses* slow the rate (by 50%), but increase the depth and force of the respiration, particularly of inspiration. The volume of the individual respirations is therefore increased (by 40%). The total quantity of air respired in a given time is but little altered; and the CO_2 of the blood is very little increased. *Larger doses* act like morphin.

Heroin is therefore somewhat superior to morphin in cough; the more so since it is less apt to create a habit; and also because the therapeutic dose and the toxic dose lie farther apart. (Although the absolute fatal dose of heroin is smaller than that of morphin, it exceeds the therapeutic dose

200 times; whilst with morphin the difference is only 80 times, in rabbits.) The predilection of heroin for this center is so pronounced, that this action can be obtained by appropriate doses, without producing any other nervous effects. (It must be remarked, however, that these favorable results have not been obtained by all experimenters. The bulk of the evidence is certainly in favor of heroin.)

Codein, dionin and peronin are intermediate in regard to their respiratory actions, codein approaching most closely to heroin. Since these drugs are excitant in their general actions, they may increase the oxygen consumption.

(*b*) *Effects on the Circulation.*—These are quite complicated, and therefore variable; but they have little practical importance as they are only pronounced by very large doses.

The actions are presented in the following diagram:

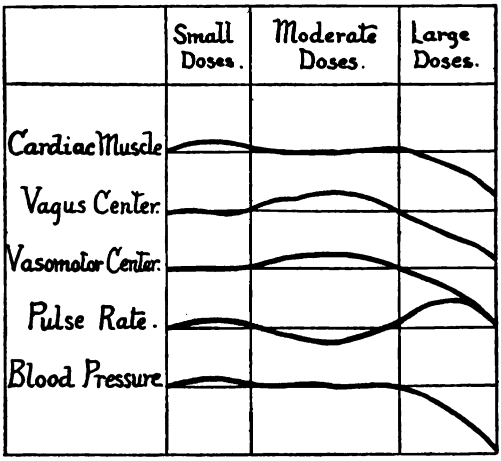

Fig. 53.—*Diagram of the Action of Morphine on the Circulation:* A rise above the abscissæ indicates an increase or stimulation, a fall below the abscissæ a decrease or depression.

Morphin affects the cardiac muscle and the vagus and vasomotor centers, all being first stimulated, and then depressed. Small doses cause a slight quickening of the pulse through stimulation of the cardiac muscle. Larger doses slow the rate through vagus stimulation, but the pressure remains normal, the slowing being compensated by the vasomotor stimulation. Large doses depress all the functions, so that the pressure falls greatly. The respiratory center, however, is paralyzed before the circulation.

There is a somewhat specific stimulation of the vasodilator center for the *cutaneous vessels* even with small doses. The skin becomes red. There is a feeling of warmth and an increased secretion of sweat. This erythema in higher grades or in susceptible individuals may lead to exanthemata.[1] With large doses the skin becomes pale, through the vasodilatation of the splanchnic area, and cyanotic from the asphyxia.

There is no proof of any direct action on the *cerebral circulation*. This will be lowered indirectly as the result of the general fall of blood pressure, if the dose has been sufficient to produce the latter result. According to Aliprandi (1905) there is a short vasoconstriction, followed by a lasting dilatation.

(*c*) *Effect on the Pupils.*— In man, morphin produces a very strong contraction of the pupil (miosis). This effect has no therapeutic application, but is important in the diagnosis of morphin poisoning.

The miosis occurs after systemic, but not after local application. It cannot be produced on an enucleated eyeball. It is therefore central, and is generally attributed to *paralysis of the medullary pupillo-dilator center.*

It might be due either to a stimulation of the constrictor center or to a depression of the dilator center. It is probably paralytic, for most of the other effects of morphin on the medulla are paralyzing, and the miosis persists in the highest grades of poisoning, when stimulation would scarcely be possible. Further, in those animals in which morphin has an excitant action (cat), it produces dilatation instead of contraction. In the dog, the pupillary effect is variable, but usually dilator.

(*d*) Several effects of morphin are probably, at least in part, due to its medullary action: thus, salivation, vomiting, sweating, etc. These will be considered later, since the central nervous system is only one of the factors involved. The *sweating* is mainly secondary to the dilatation of the cutaneous vessels and later to the asphyxia.

The *temperature is lowered* (sometimes this may be preceded by a slight rise). The fall may be as large as 2° C. with large doses, the extent depending, however, more upon idiosyncrasy than upon the dose. The cooling is particularly great if the animal is kept in cold surroundings. The cause of the fall is a diminished heat production, which may be reduced by 80% in extreme cases, reaching its minimum in the third hour. The heat loss is diminished (up to 20%), partly through the effort of the heat centers to compensate for the diminished production, partly through the depressed circulation.

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[1] Other poisons which may produce erythema are: atropin, quinin, chloral, coal-tar products, iodids, bromids, antitoxic sera, etc.

(C) **Effects upon the Spinal Cord.**— Morphin (also heroin, codein, and the other members of the group) stimulates the spinal cord after the manner of strychnin, increasing the reflexes, and in large doses producing convulsions. (Strychnin is therefore not a good antidote for morphin; one of the opium alkaloids, thebain, is even a typical member of the strychnin group.)

The stimulation persists even with very large doses; the convulsive dose is indeed so large that mammals susceptible to the depressant action of morphin (*e. g.*, man) die from paralysis of the higher centers before the convulsant dose is reached. In the frog, the tetanus develops so slowly that it may not appear until the paralysis of the cerebrum has lasted some hours.

The **cause of the action of morphin** on the central nervous system is very imperfectly understood, just as is that of all other alkaloids. It has been attempted to explain its action by a *change in cerebral circulation*, but this change comes late and is seen only with the largest doses. But even if this explanation were true, it would not give any real insight into the cause of the action, but only advance the question one step further: for this itself would be due to depression of the vasomotor center. The same discussion has been going on in regard to natural sleep.

Others have sought for *histologic changes*, but with the present methods, unsuccessfully. As to *gross changes* in the brain, almost all drugs which cause narcosis or tetanus are said to produce hyperemia of the membranes, often also some effusion into the ventricles.

2. Peripheral Actions.—(**a**) Morphin and other members of the group have practically *no action upon muscle- or nerve-fibers or endings.* Particular stress must be laid on the fact that the *sensory endings are in no way affected,* so that the local application of morphin or opium is entirely irrational.

But this is a practice which clinicians seem very loath to renounce, and lotions and local injections containing morphin are still very frequently employed. The apparent good results obtained are largely due to the absorption of morphin from wounds or mucous surfaces. It can even be absorbed to a slight extent from the unbroken skin. The most popular form of this local use is the lead and opium wash, and this certainly gives satisfactory results. The effects are probably to be explained by the non-irritating covering furnished by the lead precipitate, and by the astringent action of the lead itself. (The morphin is not precipitated by the lead.) The direct application of codein destroys the activity of nerve ganglia and nerve-fibers.

The application of *dionin* to the eye causes acute edema of the conjunctiva, appearing in a few minutes, and lasting several hours. This is ascribed to a dilation of the vessels. It is utilized in ophthalmology.

(b) Effects upon the Alimentary Canal.— *Stomach.*— Morphin, no matter how administered, impairs the digestion and tends to produce nausea, vomiting, and salivation.

Morphin is excreted very rapidly into the stomach, but there is no reason to assume any local irritation. The action is probably central, *i. e.,* an indication of the effect which is more fully developed in apomorphin. The emetic action is followed by depression of the vomiting center, at least in dogs, so that irritant emetics prove ineffective.

The degree of nausea varies greatly in different individuals. It is sometimes so severe, and accompanied by so much depression, that it precludes the use of morphin. It may be lessened by bromids, in some cases.

Heroin produces only salivation, with very little gastric disturbance.

Effect on Peristalsis.— Small doses of morphin lessen peristalsis in all animals; this is also the effect of larger doses in man; but the dog and some other animals react to large doses by greatly increased peristalsis. These effects are very marked.

Two explanations of the mechanism of the constipating action have been advanced. That of Nothnagel attributes the effect to stimulation of the central origin of the inhibitory splanchnic fiber. The other theory explains it by depression of the local reflex nervous mechanism (the cells of Auerbach's and Meissner's plexus) controlling peristalsis. The latter view is the more commonly accepted, but neither theory is quite satisfactory.

It is generally believed that opium is more constipating than morphin; this and some other data support the theory of peripheral action.

Nothnagel's theory (1882) is based on the following experiments, made on rabbits:

The application of a crystal of NaCl to the muscular coat of the unpoisoned intestine produces a constriction above the point of application — *i. e.,* the effect is identical with that produced by mechanical stimuli, and is, therefore, due to stimulation of Auerbach's plexus. (A crystal of KCl, on the other hand, produces a constriction ring which remains confined to the point of application, and is, therefore, myogenic in origin.) The administration of 20 mg. of morphin prevents the spreading of this reflex; but it reappears if the mesenteric nerves are divided. It is therefore assumed that the morphin stimulates some inhibitory fibers centrally. The reflex also reappears if large doses of morphin (60 mg.) are given; these would therefore paralyze the inhibitory nerves.

The theory does not explain why morphin also prevents peristalsis caused by purely locally acting drugs, such as nicotin.

The increased peristalsis from large doses of morphin is best explained by assuming a local irritation.

(c) **Secretions.**— Our knowledge in regard to this subject is also unsatisfactory. Whilst morphin generally tends to check the salivary as well as the bronchial secretions, yet the saliva is very frequently increased. When this occurs in early stages, it may be attributed to nausea, but it sometimes occurs rather too late for this explanation to hold, and it is possible that the medullary salivation center is involved. The sweat is increased through the cutaneous hyperemia. Heroin also increases saliva and sweat.

The *appetite* is diminished on account of the lessened perception of hunger and through gastric derangement.

(d) **Metabolism** is also lessened on account of the quiet condition of the animal and, in prolonged observations, on account of the disturbed digestion. The CO_2 is increased in the blood through the asphyxia. The nitrogen excretion is also lessened, but the ratio of urea to total nitrogen is not altered. That the lessened output of CO_2 is really due to depression is shown by the fact that it is increased in the cat and by the stimulating members of the group (codein). The urine often reduces copper, from the presence of morphin-glycuronic acid. Glycosuria also arises from the asphyxia. The *leucocytes* of the blood are diminished in morphin poisoning, acute or chronic.

III. ABSORPTION, FATE, AND EXCRETION.

Morphin is readily absorbed from all surfaces, and to some extent even from the unbroken skin. Its further fate was for a long time problematic. Although contradictory claims have been made, it is now conceded that only the very faintest traces, if any, are excreted through the urine. Nor does this contain any morphin derivatives. Recent investigations have shown that after hypodermic injections up to 66% is excreted through the saliva and gastric juice, and especially through the intestine. This large percentage holds only for acute poisoning. It is very much reduced in chronic poisoning, as will be described under that heading.

Some of the morphin is also excreted by the milk and may cause morphinism in sucklings. The rest is decomposed in the body.

The excretion by the alimentary canal is very rapid; morphin can be discovered in the saliva within three minutes after a hypodermic injection; it disappears again from the stomach in about an hour. The morphin disappears from the blood within twenty minutes, but is not destroyed in this fluid. A considerable amount is fixed by the lipoids of the nervous tissues, and by the liver, and is there gradually destroyed by oxidative processes. It disappears entirely from the body within two days (Cloetta, 1903).

Of *codein* about 80% is excreted unchanged, mainly by the urine, but some also by the feces. Repeated administration does not lead to increased destruction, nor does it appear to produce tolerance of this alkaloid.

The substances which cause the characteristic odor of opium are excreted largely by the urine, and to some extent also by the breath, sweat, and milk.

IV. PRINCIPAL DIFFERENCES AMONGST THE IMPORTANT MEMBERS OF THE GROUP.

Morphin produces the greatest narcotic, analgesic and hypnotic and intestinal actions, and has the least stimulant effect. It causes the greatest derangement of digestion and is most apt to induce a habit.

Heroin has a specific effect upon respiration. In other respects it is more stimulating and less narcotic, and it acts less upon the alimentary canal.

Codein, Peronin, Dionin and Narcotin are intermediate between morphin and heroin. *Dionin* has a specific action on the conjunctiva. *Narcein* is practically inactive. *Thebain* acts like strychnin.

The members of the **protopin group** (protopin, cryptopin, chelidonin, homochelidonin, and chelerythrin), which are found to some extent in opium, but especially in other Papaveraceæ, cause paralysis of the sensory endings in the manner of cocain. They also produce a paralytic change in the striped muscle endings, so that stimulation with interrupted current only produces a series of very rapid and complete contractions and relaxations instead of a continuous tetanus. The heart muscle is also depressed, so that the heart is weak and slow. The respiration is stimulated. These drugs have little or no therapeutic importance.

A preparation of sanguinaria examined by the author had very little action on the heart, and was purely depressant to the central nervous system, the reflexes being diminished, the respiration slow and shallow, and death occurring through respiratory paralysis. No secondary tetanus was noticed on the frog. Other observers have noted nausea and violent peristalsis, with very little central depression. This interesting drug requires further investigation.

Relation of Chemic Structure and Action.—The narcotic actions of morphin are connected with the two OH groups of its molecule. When these are replaced by other chains (as in heroin or codein), the strychnin action predominates; this convulsive action increases with the size of the molecules which are introduced. The alkaloids of opium belong to two chemic groups: Morphin, Codein, Pseudomorphin (Oxydimorphin), and Thebain being derived from the base *Morpholin;* whilst Papaverin, Narcotin, and Narcein are derivatives of *Isoquinolin.* Notwithstanding this chemical difference, the actions are qualitatively very similar.

Relation to Other Groups.—The morphin group is closely connected with a number of other groups: with *strychnin* through its spinal action; with *alcohol* through its narcotic action; with *Cannabis Indica* through the cerebral effects; with *cocain* through the protopin group; with *apomorphin* through its composition and the subordinate emetic action.

V. CHRONIC OPIUMISM.

Whilst the therapeutic use of opium dates back of Hippocrates, its habitual use seems to be of more recent origin. The first authentic records fall in the beginning of the sixteenth century. It would seem that its use is much older in India than in Turkey, and that the Mohammedans learned it through the conquest of the former country. Their acquaintance with cannabis indica is of much earlier date. The existence of the opium habit was at first confined to the Orient; its introduction into Europe and America is of very modern date.

Opium users introduce the drug in three different ways: by smoking, by eating, or by hypodermic injection of morphin. *Smoking* is the form mainly practised in the East, and is not uncommon in the United States.

Smoking-opium (chandoe) is prepared by the Chinese, by a complicated process of roasting, and repeated extraction and evaporation. Its morphin-content is about the same as that of ordinary opium; but it is claimed that the opium smoke does not contain morphin (*e. g.,* Hartwich and Simon, 1903). This statement needs confirmation, in view of the close agreement of the effects of opium smoking with those of morphin. The smoking, however, produces a more pronounced psychic stimulation, a form of intoxication, differing from that of alcohol in that it causes greater energy, vividness, and sharpness of imagination. The half-conscious victim is removed from the unpleasant reality into a realm of glowing fancy, accompanied by lethargy. This rather pleasant condition is not lasting; the patient awakens in a few hours to sensations similar to those following an alcoholic excess, but much worse. To escape these, he is apt to resort to more of the poison.

The ultimate consequences of opium smoking are the same as those of the other forms of opium habit. They do not develop as rapidly, partly because the quantity consumed in smoking is necessarily more moderate.

This description of the bad effects applies mainly to the European races. Curiously enough, Eastern races are not affected in the same way. They smoke opium more as a European smokes tobacco. Though, of course, incapable of doing work while under the influence, the lethargy need not last longer than half an hour, when they can resume their business. Nor do they show the moral degenerations so striking in the Western users.

The danger of falling into the opium habit is not equally great for all persons. Besides the individual differences in the moral sense, will power, etc., those who are pleasantly stimulated by morphin are naturally more exposed to its dangers than those who are affected unpleasantly; but the danger exists for all, and must be constantly in the mind of the physician when he prescribes these drugs.

When opium or morphin are taken *by the mouth or hypodermically,* the effects on the imagination are much less pronounced. These forms of morphinism cannot even boast of the delusive pleasures of smoking, though it cannot be denied that opium, even when taken by the mouth or through the skin, produces at first the somewhat negative pleasure which consists more in a brutish indifference to surroundings than in any actual enjoyment. In smaller doses the capacity for enjoyment may even be increased, just as with alcohol, by removal of the ordinary restraining impulses. But, not to mention the final cost, even this pleasure soon fades, and ere long the famed dreams of the opium eater degenerate into nightmares quite as bad as those of delirium tremens. The opium eater now takes his drug not because he wants it, but because he cannot get along without it. When it has once taken a thorough hold, morphinism must be considered not so much as an indulgence, a pleasure, or a vice, but as a real disease. The organism having become accustomed to working under its influence, revolts in a very violent manner against its withdrawal. A remarkable *tolerance* to the poison is acquired, so that morphin victims consume quantities which would be surely fatal to ordinary individuals.

The *daily consumption* of morphin is generally about 0.5 Gm.; but as much as 5.5 Gm. (85 grains, or one and two-thirds of the ordinary bottles) has been reported. Even larger doses are claimed by patients; but their statements are generally unreliable, since they are made in the hope that the drug will be withdrawn more gradually.

However, there can be no question that extraordinarily large doses can be taken daily without producing acute symptoms, and are even necessary to prevent the withdrawal symptoms. This immunity to morphin is, however, never absolute, and death from overdoses forms the most frequent "excitus letalis" of the morphinist.

The abstinence symptoms are something very difficult to explain, and so far they have been demonstrated only with opium and cocain; the delirium tremens of alcoholics may be a similar phenomenon.

Explanation of the Acquired Tolerance to Morphin.— Marmé believed that morphin was transformed in the body into a substance, oxydimorphin, with exactly opposite actions. This substance, he supposed, produced the abstinence symptoms; required the introduction of increasing amounts of morphin to neutralize its effects; and in turn neutralized the morphin, accounting in this way for the tolerance. This hypothesis is not supported by facts; the morphin is not transformed into oxydimorphin, at least to any extent; and *the actions of oxydimorphin* do not agree with those assumed by Marmé. It has no narcotic effect. If it is introduced hypodermically, or if it is injected slowly by a vein, it is absolutely inactive, because it is rapidly destroyed in the alkaline media of the body. This rapid destruction speaks strongly against its being concerned in the morphin habit. If it is injected suddenly into a vein, it causes vomiting, diarrhea (which is often bloody), and death by paralysis of respiration.

It has been claimed repeatedly that the serum of animals habituated to morphin protects other animals against this poison. This statement has no foundation in fact.

The tolerance is explained by the *increased power of the organism to destroy the poison.*

Faust, in a recent research on this subject, recovered from the feces of a dog 66% of the morphin administered hypodermically, when the poisoning was acute. In the feces of the twenty-first to twenty-fourth day of the administration he only recovered 26%; from twenty-nine to thirty-two days, 8%; from thirty-six to forty days, 4%; and if still longer continued, none at all; and this notwithstanding the fact that the later doses were very much larger than the original doses (fifty times the original amount). Incidentally, he found exactly the same symptoms of chronic morphinism in the dog as exist in man. The animals showed signs of uneasiness for the morphin, they became very restless when the time for the injection approached, and one dog gave every sign of satisfaction when the syringe was introduced. Tolerance was soon established, so that after twenty days a dose ten times as large as that which originally gave a very strong effect had little action. Rabbits and goats also acquire tolerance; whereas frogs seem to become more susceptible.

According to Bouma (1903) the continued administration of *codein* does not lead to increased destruction, nor to tolerance. (Cloetta (1903) has contradicted the statements of Faust.)

Symptoms and Effects of the Opium Habit.— The later *consequences of opiumism* are insidious, but none the less dangerous. For years, victims of the habit may appear quite normal to superficial observers, but closer attention would even then reveal signs of the disease. The physical consequences relate at first to the digestive tract. There is obstinate constipation, alternating later with equally obstinate diarrhea. There is loss of appetite alternating with voracious hunger and thirst (polydipsia), and polyuria. These disturbances of digestion, as well as the more direct action of the drug, are not long in showing their effects upon the rest of the body. The patient loses flesh rapidly and suffers from marasmus and cachexia.[1]

There is a peculiar cirrhosis of the skin, which becomes pale, dry and rough. The nails, teeth and hair are also diseased. The condition of the integument is rendered still worse by the local effects of the injection when the drug is used hypodermically. The whole skin may be mottled with scars and marks of recent or older injections, and abscesses are often produced through want of cleanliness. Even when the drug is used by the mouth, the entire skin often acquires a peculiar waxy appearance.

The pupils are almost invariably contracted; the eyes lose luster; so that an opium user may often be recognized from his appearance. The pupillary and accommodation movements are affected. The *heart* is irregular. *Albuminuria, glycosuria, amenorrhea,* and impotence are frequent. *Fevers* resembling simplex, intermittent, and typhoid, are often seen. The *motor-nervous system* shows considerable change: nervous tremors, increased reflex irritability, etc. These conditions sooner or later weaken the resisting powers of the patient, so that he falls an easy prey to some other ailment, and thus rarely reaches old age.

The effects of the opium habit upon the *character* of the patient are even more deplorable. This soon sinks to the very lowest level. With a certain amount of low cunning he combines a total unscrupulousness, and it is very doubtful whether the testimony of an opium user can ever be accepted, even in instances which do not affect him. He becomes absolutely incapable of any effort. Duty no longer appeals to him, and in order to escape it, or, still more, in order to obtain his drug, he will resort to any lie or any trick, no matter how dishonest. He will promise everything and fulfil nothing. Were he not so cowardly and disinclined to, or rather incapable of, any effort, he would be fit for any crime. His condition is all the more unhappy since he fully realizes it and sees himself in his true colors. He makes grand plans, and, at the same time, knows that he can never summon the energy even to begin them. Add to this the fact that he is a social outcast, and it is difficult to imagine a more unhappy condition. To the physician he should appeal as a sufferer, as one afflicted with a form of insanity; one who, like any other insane patient, should be treated with unflinching firmness, but with the most considerate kindness. Only in this way will it be possible to help him. He is himself devoid of the necessary will power, and this must to some extent be supplied by his physician and attendants. In this connection, as in the other drug habits, suggestive therapeutics offers a promising prospect.

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[1] These are two ill-defined terms. The former, marasmus, signifying a continued low condition of the nutrition and a wasting of the flesh without apparent organic cause. Cachexia also indicates a wasting of the body, with some striking change in the features, which are usually pinched and yellow.

Abstinence Symptoms.—The withdrawal of morphin from those accustomed to its use leads to a train of very severe effects, the severity being proportional to the rapidity with which the drug is withdrawn. Prominent throughout is an almost uncontrollable craving for the drug, passing sometimes into a true mania. Besides this, the first symptoms consist in spasmodic yawning and sneezing; coryza and lachrymation; and hoarseness. The pupils dilate again. The extremities are cold, the head congested. Headache, neuralgias, and violent pains, often in the legs. The digestion is profoundly disturbed, presenting the symptoms of a violent functional gastroenteritis. Insomnia is a very constant symptom; the patients are very irritable and excitable, and this condition may culminate in delirium or acute mania, often suicidal. Women often have hysteric attacks. The most dangerous phenomenon is sudden collapse, ushered in by rapid, irregular and weak pulse, cold sweat, and general prostration; and often ending fatally by heart-failure. This collapse, if severe, demands the prompt injection of a moderate dose of morphin, which generally causes the symptoms to disappear.

The ordinary medical **treatment of the opium habit** consists in *removal of the drug; and supporting and symptomatic measures.* The **removal** must be done with great care, and is best carried out in special institutions, where a careful surveillance of the patient is possible, both to prevent his obtaining an extra supply of the drug, and to be able to control the symptoms. It has been attempted to stop the habit by removing the drug suddenly; by very gradually diminishing the doses; and by diminishing the dose quite rapidly. The first is useless cruelty, and may even be dangerous. The second does not usually accomplish the desired result. The last is certainly the best. According to this method, the drug is removed just as rapidly as can be borne by the patient without producing any very violent reaction. No iron-clad rule can be followed by which this reduction may be accomplished. At the same time the system is built up by proper *hygienic measures.* The appetite often needs to be sustained by bitters and other tonics. Sleeplessness is a very frequent complication, and must be met by bromids, chloral, or some of the hydrocarbon hypnotics. To combat morphinism by cocain, codein, heroin, or other drugs which merely replace the morphin habit by some other habit equally bad, is of no benefit to the patient. Thorough cleansing of the bowels with emetics and cathartics at the beginning of the treatment is very useful, and it is perhaps to this that pilocarpin owes its success. This drug has been employed on the theory that it removes the hypothetic decomposition products. As far as may be judged, it has given good results, whatever the explanation. Pilocarpin, strychnin, atropin, and scopolamin are used in the symptomatic treatment of all drug habits. Scopolamin (hyoscin) appears to permit a more rapid withdrawal of the morphin. *Suggestion* may sometimes be a great help in preventing relapses.

The cure is rarely permanent. Patients usually drift into the morphin habit to relieve some existing condition,—*e. g.*, sciatica,—and this condition will, of course, reappear when the morphin is removed and incline them to resume its use. And besides, persons who have once been morphinists show by that fact that they are more apt than normal individuals to succumb to the dangers that originally overcame them.

Opium habit in children is unfortunately not at all rare, and it is usually started by the indiscriminate employment of paregoric and other soothing syrups. They present the typical symptoms already described. Withdrawal of the medicine is followed by restlessness, wakefulness, and every indication of suffering and distress. The treatment would be mainly hygienic.

The morphin derivatives (*Heroin, Dionin, etc.*) may also give rise to habit, resembling in every respect that of morphin. The danger is, however, much less; partly because they do not possess the desired narcotic action. A case of *codein habit* has been reported by Pelz (1905). The phenomena were strictly analogous to morphin, including tolerance.

VII. TOXICOLOGY OF MORPHIN AND OPIUM.

Opium is a very frequent means of suicidal poisoning, and accidental overdoses are not at all rare. It is, however, one of the rarer poisons in criminal cases, since its action is so slow and the symptoms so typical.

Symptoms.—To sum up the symptoms of morphin- or opium-poisoning from a toxicologic point of view, the first to be noticed are giddiness, confusion, and stupor, this terminating gradually in complete insensibility. The respiration is slow, the pulse full, slow, and laboring, eyes closed, pupils usually contracted and insensible to light, and the face red.

As the poisoning advances the skin becomes pale and cold, and moist with perspiration, the lips are livid, the breathing slow and stertorous, the pulse feeble and almost imperceptible, the limbs relaxed; but death is sometimes preceded by asphyxial convulsions.

The symptoms usually appear in from ten minutes to one hour after the drug has been taken by the mouth; perhaps half an hour is the most common. Death occurs in from two to twelve hours.

If the patient *recovers,* there is a great deal of persisting nausea, nervousness, and headache. With therapeutic doses, however, the patient may awaken refreshed. Recovery is possible even when convulsions and coma have set in. The former disappear and the coma gradually passes into a long sleep, often lasting from twenty-four to thirty-six hours.

On account of the treatment, it is extremely important to establish the **differential diagnosis of the origin of a coma.**[1] Those forms the coma which might be confounded with morphin are: alcoholic (chloral), uremic and diabetic, epileptic, and apoplectic.

One of the most important points is furnished by the **pupils.** If these are *dilated,* the coma is probably *alcoholic,* but may be diabetic. With *pin-point pupils* the coma is either from *opium* or *pontine apoplexy.* If the latter, they are very often unequal, and on lifting the arms, one may often detect a paralysis.

The pupils respond readily to light in epileptic coma, not in the others.

Just before death the pupils may become dilated from the asphyxia. (In the dog the pupils are usually dilated throughout the poisoning.)

The *smell of the breath* furnishes presumptive evidence of *alcohol*-poisoning, but it is not a definite proof, since this substance is often given as an antidote, and is so often present in quantities which would not cause a coma. The smell is, however, usually characteristic of *opium, uremia,* and *diabetes,* but not of morphin. Uremia would also be characterized by *albumin in the urine.*

There are yet other forms of coma which may be confused with these, but no rules can be laid down for them. The history is often of the greatest importance.

The *autopsy* shows nothing characteristic. There are the usual phenomena of asphyxia. The pupils are variable. The mucous membrane of the stomach is sometimes reddened. If the poisoning has been by opium, one may discover its characteristic odor.

Treatment of Acute Opium-poisoning.— The first indication is to *empty the stomach,* and this no matter whether the drug has been taken by the mouth or hypodermically. If narcosis has already set in, emetics may act too slowly, and it may be necessary to employ a stomach-pump. The best *chemic antidote* is *potassium permanganate.*[2] The patient should be kept awake as far as possible and in *con-*

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[1] Coma: A condition of insensibility from which the patient cannot be aroused.

[2] De Buscher (1904) has found this effective in rabbits, even when it was administered three hours after the morphin; it was much less successful with dogs.

stant movement, since this contributes to the better tone of the medullary center. Other *general reflex stimulants* may be employed, such as *cold ablutions,* the inhalation of *ammonia* in the form of smelling salts, hypodermic injections of ether, etc. Caffein, especially in the form of strong, black, hot *coffee,* is the best physiologic antidote.

Atropin has been used extensively and somewhat indiscriminately *in the treatment of morphin poisoning.* It is a very dangerous remedy in this condition. The most conspicuous antagonistic actions of these two poisons are on the pupil, heart-rate, psychic processes, secretions, etc.—in short, upon functions which are of very subordinate importance in dangerous cases of poisoning. Any useful antagonism must be sought in their actions on the circulation, respiration, and metabolism. A careful study will show that the effects of morphin and atropin on these functions are antagonistic only with certain stages; whilst more severe grades are actually synergistic. The later paralytic effects of atropin coincide with those of morphin; whilst in the last stages of morphin poisoning the centers are too greatly depressed to respond to the slow and weak stimulation of atropin. *The usefulness of this antidote exists therefore only if moderate doses of atropin are given in moderate morphin poisoning* (or vice versa). This conclusion is supported by several series of experiments on animals. As a practical deduction, the atropin should be given in the *dose* of 1.5 mg. (1/40 gr.) and this should *not* be repeated.

A general antagonism exists also between morphin and small doses of *cocain,* especially as regards the effects on temperature and metabolism. Larger doses are synergistic, and as the susceptibility to cocain is variable, the hypodermic *dose* of 0.01 Gm. (1/6 grain) should not be exceeded.

The patient should be kept *warm.* If the breathing shows signs of failing, artificial respiration should be supplied.

When the danger is over, the *constipation* which usually follows should be relieved by cathartics and enemata.

The *fatal dose* of morphin for man is, on the average, 0.2 to 0.4 Gm. (3 to 6 grains); or of opium, 3 Gm. (45 grains).

It is important to remember that *children are much more susceptible* to the drug than adults (allowing for the weight).

Young rabbits, guinea pigs, and dogs are also more susceptible than the full grown animals, whereas kittens are rather more tolerant than adult cats. Amongst the *different animals,* man is by far the most susceptible, the fatal dose by subcutaneous injection being about 1/50 of that required for the same weight of rabbit, 1/70 of the dog's, and 1/100 for the pigeon.

The possibility of *idiosyncrasy* must be borne in mind: as little as 0.2 Gm. (3 grains) of opium (=½ gr. morphin) is said to have been fatal in one case. 0.3 mg. ($^1/_{200}$ grain) of opium is reported as fatal in two cases in children (quoted from Lewin).

VIII. THERAPEUTICS.

Morphin and opium are drugs which are used against *conditions,* and not against *diseases; i. e.,* they may be employed in almost any disease if the conditions demanding them arise.

The conditions indicating morphin are mainly the following: *to lessen pain, to produce sleep, to check peristalsis, and to suppress cough.*

1. Pain.— Since the lessening of pain is its first effect, small doses only should be employed for this purpose. It will be remembered that it is effectual especially against persistent pain, and in this it is almost specific, surpassing in analgesic action any other drug. The local application is without effect. As an analgesic morphin, especially hypodermically, has the preference over opium.

2. Insomnia.— Morphin will be useful especially when this is produced by pain, but not when it is the result of nervousness. Besides its superior analgesic properties it surpasses chloral in not affecting the circulation. The two are very usefully combined.

Some of the **disadvantages of opium** are: the tendency to constipation, to nausea, or gastric disturbances; and in some individuals it has an excitant action instead of being hypnotic. In insomnia one must be ever mindful of the danger of the formation of a morphin habit.

3. Peristalsis.— Opium especially is extremely useful in diarrhea due to acute intestinal catarrh. By checking the peristaltic movement, it gives a chance for rest and repair, and thus leads to permanent cure.[1] It is one of the most important ingredients of the so-called cholera-mixtures. In the constipation of lead-poisoning which is due to tetanic contraction of the intestine, it relieves this spasm, and with it the pain. It is also very useful in *peritonitis* in relieving the pain, both directly and by lessening the movements of the intestines which are giving rise to it.

4. Cough.— Morphin and other members of the group depress the sensibility of the respiratory center to reflex stimulation, and morphin also diminishes the amount of bronchial secretion.

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[1] Tyrotoxicon-poisoning is an exception, for in this morphin is only harmful.

In bronchitis the cough is caused by reflex stimulation of the center. The patient also involuntarily uses the shallow respiration, since deep respiration brings on coughing. These conditions are removed by members of the morphin series, which at once lessen the tendency to coughing and affect the respiratory center in such a way as to slow and deepen the respiratory movements. As to particular members of the group, codein was formerly often used because it is devoid of the intestinal action of morphin. In recent years it has been superseded by heroin, as this causes no headache or gastric disturbances and presents the least danger.

When the bronchial secretion is extremely abundant, morphin may be contraindicated, for then the cough fulfils a useful function in cleansing the air-passages.

Morphin is frequently of considerable usefulness in *asthma* by relieving the distress of the patient, and perhaps also by diminishing the reflexes which give rise to this condition.

5. Other Uses of Morphin.— Morphin is very useful as an introduction to *general anesthesia,* given hypodermically in a dose of 0.01 Gm. ($\frac{1}{6}$ grain), one-half hour before the administration of the anesthetic. It lessens the amount of the anesthetic necessary. It is very often mixed with a small dose ($^1/_{100}$ grain) of atropin, the latter for the purpose of paralyzing the vagus endings in the heart (see Atropin).

Psychic exaltations — *e. g.,* delirium tremens or atropin-poisoning — require very large doses, which might become dangerous. It may, however, be used in atropin-poisoning, whereas in delirium tremens it would not be indicated because it itself increases the nervousness.

It is used in *tetanus* for the purpose of removing the pain.

Morphin forms quite an efficient *diaphoretic.* For this purpose it is best given combined with ipecac in the form of *Dover's powders* against *colds,* etc. (See Chapter XII, M). Heroin, on the other hand, is recommended against the night-sweats of phthisis.

Morphin has also been used as an *anti-emetic.* It may be conceived that it is of benefit in depressing the vomiting center, but it is quite uncertain, and may itself produce emesis. Some members of the group are even used as emetics, *e. g.,* **sanguinaria,** but this drug also contains an irritant principle, which no doubt contributes to its action. Sanguinaria is useful as a *nauseant expectorant* in cough, where it also depresses the respiratory center.

Opium is also employed as a *styptic* to stop hemorrhage in inaccessible situations. Its action can be explained by the lessening of movements which it favors, and consequently the easier formation of clots.

Morphin is also useful in *phthisis,* through its action on the cough, bronchial secretion, and hemorrhage; and in *fever,* through its diaphoretic and hypnotic action. It has also been used in *malaria,* but with doubtful results.

The use of opium in **diabetes** is instructive in showing that a drug may relieve not only one, but several, symptoms of a disease, and still be only symptomatic, and not curative.

Good clinical observers claim that the thirst, polyuria, glycosuria, and itching of the skin are all markedly diminished. Part of this action must be attributed to the analgesic effect, while the influence on the glycosuria is due to its action on digestion, and is produced in the same way as by a limitation of the diet or by nauseants. As a matter of fact, opiophagic diabetics die faster than others. Codein has been used instead, but without any marked advantages.

IX. MATERIA MEDICA.

Opium (U. S. P., B. P.).—*Opium* (Meconium, Thebaicum).—The dried milky juice exuding from the excised unripe[1] seed capsules of the poppy, *Papaver somniferum,* Papaveraceæ. Asia and Egypt, cultivated. Fair samples have also been obtained from plants cultivated in California and Minnesota, but the price of labor makes its production unprofitable. The plant is often cultivated in gardens. The proportion of active ingredients varies greatly in different samples.

The *capsules* (Papaveris Capsulæ, B. P.) and *seeds also* contain the active principles, and are sometimes used. The seeds contain, in addition, 50% of a bland fixed oil, which may be used like olive oil.

Alkaloids: Morphin. Official requirement (U. S. P.): Not less than 9% in moist opium, 12 to 12½% in powdered, granulated, and deodorized opium; B. P., 9½ to 10½% in dried opium.
Codein, 0.2 to 0.7%.
Thebain, 0.15 to 1% (belongs to strychnin group).
Narcein, 0.02 to 0.7%.
Papaverin, 1%.
Narcotin, 1.3 to 10%.

Meconic and lactic acid, gums, resins, fats, odorous principles. No starch or tannin.

Dose: 0.015 to 0.12 Gm. (¼ to 2 grs.) (0.1 Gm. = 1½ grs., U. S. P.).

Preparations:

Opii Pulvis (U. S. P.).

Opium Deodoratum (U. S. P.).—The opium is exhausted by petroleum benzin and mixed with milk-sugar so as to contain 12 to 12½% of morphin. The purpose of this manipulation is to remove the odorous principles.

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[1] Unripe poppy capsules contain about eight times as much morphine as the ripe (Cæsar & Loretz, 1902).

Opium Granulatum (U. S. P.).—Used in manufacturing. The *dose* of powdered, granulated, and deodorized opium is 0.015 to 0.12 Gm. (¼ to 2 grs.) (0.065 Gm. = 1 gr., U. S. P.).

Preparations Containing Crude Opium.

Pilulæ Opii, U. S. P.: Each 1 grain of opium (0.065 Gm.).

Pulvis Ipecacuanhæ et Opii, U. S. P. (*Pulvis Ipecacuanhæ Comp.*, B. P.) contains 10% each of opium and ipecac. *Dose:* 0.3 to 1.0 Gm. (5 to 15 grs.) (0.5 Gm. = 7½ grs., U. S. P.).

Trochisci Glycyrrhizæ et Opii, U. S. P.: Each contains 5 mg. (= 1/12 gr.) of opium.

* *Pilulæ Opii et Camphoræ*, N. F.: Each 1 grain of opium and 2 grains of camphor.

* *Pilulæ Opii et Plumbi*, N. F.: Each 1 grain of opium and 1 grain of lead acetate.

Pilula Plumbi cum Opio, B. P., contains 12.5% of opium. *Dose:* 0.1 to 0.25 Gm. (2 to 4 grs.).

Pilula Saponis Composita, B. P., contains 20% of opium. *Dose:* 0.1 to 0.25 Gm. (2 to 4 grs.).

Pulvis Kino Compositus, B. P., contains 5% of opium. *Dose:* 0.3 to 1.3 Gm. (5 to 20 grs.).

Pulvis Cretæ Aromaticus cum Opio, B. P., contains 2.5% of opium. *Dose:* 0.5 to 2.5 Gm. (8 to 40 grs.).

Suppositoria Plumbi Composita, B. P., contain 1 grain of opium.

Other Solid Preparations of Opium.

Extractum Opii (U. S. P., B. P.). Made with water; contains 20% morphin (U. S. P., B. P.) *Dose:* 0.008 to 0.06 Gm. (⅛ to 1 gr.) (0.03 Gm. = ½ gr., U. S. P.).

Emplastrum Opii (U. S. P. = 6% of the extract; B. P. = 10% of opium).

Solutions of Opium, U. S. P.

The following U. S. P. preparations all contain 10% of powdered opium (1.25% of morphin) and have a *dose* of 0.2 to 1.2 c. c. (3 to 20 ♏) (0.5 c. c. = 8 ♏, U. S. P.); all are miscible with water or alcohol:

Tinctura Opii (Laudanum): Made with one-half alcohol.
Tinctura Opii Deodorati: Made with one-fifth alcohol after exhaustion by petroleum benzin. (This is similar to McMunn's Elixir and other patent preparations.)
(See Opium Deodoratum.)
Acetum Opii.
Vinum Opii (Sydenham's Laudanum).

Compound Liquid Preparations Containing Opium.

For Internal Use:

Tinctura Ipecac. et Opii, U. S. P.: Opium and ipecac each 10%; one-half alcohol. *Dose:* 0.2 to 1 c. c. (3 to 15 ♏) (0.5 c. c. = 8 ♏, U. S. P.).

Syrupus Ipecac. et Opii, N. F. (Dover's syrup): Each dose, 4 c. c. (1 drachm) = 0.35 Gm. (5 grains) of Dover's powder or .03 Gm. (½ grain) each opium and ipecac.

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* Not official

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Tinctura Opii Camphorata, U. S. P. (Paregoric): 4 c. c. (1 drachm) = 0.016 Gm. (¼ grain) opium. This is the preparation of opium usually given to children in the following doses: For a child two days old, 2 drops; five days old, 5 drops; one week old, 6 drops; one year old, 10 drops; two years old, 12 drops; ten years old, one-half teaspoonful; adults, one teaspoonful (8 c. c. = 2ʒ, U. S. P.).

For External Use:

Lotio Opii et Plumbi, N. F.: Lead acetate, 4.5 Gm.; Tinct. opium, 9 c. c.; water q. s. 250 c. c.

Liquid Opium Preparations of the British Pharmacopœia.

Extractum Opii Liquidum: contains 0.75% of morphin. *Dose:* 0.6 to 2 c. c. (10 to 30 minims).

Tinctura Opii (Laudanum): contains 0.75% of morphin. *Dose:* 0.6 to 2 c. c. (10 to 30 minims).

Tinct. Opii Ammoniata: contains 0.125% of morphin. *Dose:* 2 to 4 c. c. (½ to 1 drachm).

Tinct. Camphoræ Composita (Paregoric): 1 fluidrachm = ¼ grain of opium. *Dose:* 2 to 8 c. c. (½ to 2 drachms).

Linimentum Opii: contains 0.375% of morphin.

Morphina (U. S. P.).— $C_{17}H_{19}NO_3 + H_2O$.— Prepared from opium. Soluble in 3330 parts water, 4464 ether, 168 alcohol; more freely in acetic ether or amyl alcohol.

Morphin Salts: The *dose* of these is 8 to 15 mg. (⅛ to ¼ gr.) (15 mg. = ¼ gr., U. S. P.). The following are official:

	1 part soluble in water	1 part soluble in alcohol
Hydrochloridum (U. S. P., B. P.).— $M.HCl + 3H_2O$	17.2	42.
Sulphas (U. S. P.).— $M_2.H_2SO_4 + 5H_2O$	15.3	465.
Acetas (U.S.P., B.P.).— $M.C_2H_4O_2 + 3H_2O$	2.25	21.6
Tartras (B. P.).— $M_2.C_4H_6O_6 + 3H_2O$	11.	insoluble

* *Syrupus Morphinæ Compositus,* N. F.— (For Cough.)

4 c. c. (1 drachm) = Morphin sulphate 0.0022 Gm. = 1/30 gr.
Ipecac ....0.008 " = ⅛ gr.
Senega ....0.4 " = 6 grs.
Rhubarb ....0.064 " = 1 gr.

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* Not official.

Morphin Preparations of the British Pharmacopœia.

	Strength per Cent.	Dose.	
		Metric.	Apothecaries'.
Liquor Morphinæ Acetatis......	1	0.6 to 3 c. c.	10 to 50 min.
" " *Hydrochloridi*	1	" "	" "
" " Tartratis	1	" "	" "
Injectio Morphinæ Hypodermica, 1% of tartrate................		0.12 to 0.3 c. c.	2 to 5 min.
Suppositoria Morphinæ, each ¼ grain			
Trochiscus Morphinæ, each 1/36 grain			
Trochiscus Morphinæ et Ipecacuanhæ, each 1/36 grain......			
Tinctura Chloroformi et Morphinæ Composita.............	1	0.3 to 1.0 c. c.	5 to 15 min.

Codeina (U. S. P., B. P.).— Methyl-morphin, $C_{17}H_{18}(CH_3)NO_3 + H_2O$. The *dose* of the alkaloid and its salts is 0.015 to 0.12 Gm. (¼ to 2 gr.) (30 mg. = ½ gr., U. S. P.).

	1 part soluble in	
	water	alcohol
Codein	88.	1.6
Phosphate (U.S.P., B. P.).— Cod.$H_3PO_4 + 2H_2O$	2.25	261.
Sulphate (U. S.P.).— Cod.$_2H_2SO_4 + 5H_2O$.	30.	1035.

Syrupus Codeinæ (B. P.).— 1 fluidrachm = ¼ grain codein phosphate. *Dose:* 2 to 8 c. c. (½ to 2 drachms).

* **Narcotin.**— *Dose:* 0.2 Gm. (3 grs.).

* **Heroin** (Diacetyl-morphin).— Soluble in water on the addition of a trace of acid (acetic). *Dose:* 0.005 to 0.01 Gm. (1/12 to ⅙ grain).

* **Heroinæ Hydrochloridum.**— A white powder, is freely soluble in water. The incompatibilities of heroin and dionin are those of alkaloids in general.

* **Dionin.**— Ethyl-morphin Hydrochlorid.— A white bitter powder, soluble in water and alcohol, insoluble in ether and chloroform. *Dose:* 0.015 to 0.02 Gm. (¼ to ⅓ grain). In ophthalmology it is applied as a 10% ointment in trachoma, chronic conjunctivitis, etc., for its irritant action.

Sanguinaria (U. S. P.).— *Blood-root.*— The rhizome and rootlets of *S. canadensis,* Papaveraceæ. North America. Sanguinarin and other Alkaloids of the protopin series; berberin (which causes the color); resins.

Preparations (not miscible with water):

Fluidextractum S. (U. S. P.).— Diluted acetic acid. *Dose:* 0.06 to 0.3 c.c. (1 to 5 minims) (0.1 c. c. = 1½ ♏, U. S. P.).

Tinctura S. (U. S. P.).— 10%; two-thirds alcohol, acidified. *Dose:* 1 to 2 c.c. (15 to 30 minims) (1 c. c. = 15 ♏, U. S. P.).

* Not official.

* **Chelidonium.**— *Celandine.*— The root of *Chelidonium majus*, Papaveraceæ. Naturalized in North America. Chelidonin $C_{20}H_{19}NO_5.H_2O$, alkaloids of the protopin series and berberin, which causes the color. *Dose:* 1 to 4 Gm. (15 to 60 grs.).

The fresh (red) juice is irritant and is used popularly to remove warts.

(B) CANNABIS INDICA AND SIMILAR DRUGS.

In this rather heterogeneous collection, a number of drugs have been placed, bearing a more or less close resemblance to morphin in their action upon the brain, but otherwise sufficiently different to prevent their being placed in the same or any other group; namely, Cannabis indica, Anhalonium and other cactus products, Lactucarium, and Lupulin.

They have no therapeutic importance. Since their action is largely a psychic one, which cannot be completely investigated on animals, they are very little understood.

Cannabis Indica.— This drug has, at least in this country, a theoretic rather than a practical importance. It is a powerful stimulant of the psychic functions, and is much used in the Orient for this purpose, as "Hashish" and under various other names; either the leaves of young twigs or the resin being employed. These are made into a confection or smoked with tobacco. The effect is the same in any case. The user at first becomes very happy and hilarious. Everything amuses him. He also develops very affectionate tendencies, and thoroughly believes in universal brotherhood. Soon he becomes unconscious of his surroundings. His ideas scintillate, but he cannot fix his mind upon any subject. The rapid passage of ideas causes time to seem very long. The patient often has a hallucination of double personality. From this condition he gradually passes into melancholia and then into a deep sleep.

The intoxication differs from that of opium by the greater activity of movement and of imagination. The Oriental appears to be transported into his elysium and all that this implies. With Caucasians, the stimulating effect is smaller, and the aphrodisiac effect seems wanting, but the intoxication is generally of a pleasant, jolly type. It may, however, be quite short and often absent, and is always followed by melancholia and sleep. On account of the latter, the drug has been recommended as a hypnotic. It is stated that it is not fatal even in very large doses, but experience on dogs certainly shows that it presents some danger. The habit to which it gives rise shows less effect upon the alimentary canal and less marasmus than does morphin, but more often psychic alterations, dullness, or mania.

Dogs[1] also show a decided narcotic effect. After a preliminary ataxia, excitement, and nausea, the animals usually fall into a deep and prolonged sleep, during which the sensation of pain is much diminished, whilst the reflexes persist. Some animals show acute mania; a fatal ending is not rare from doses which are ineffective in other animals, the same preparation being used. Considerable idiosyncrasy exists, and the action is fairly independent of the dose. The effects cannot be obtained by hypodermic administration (on account of the non-absorption of the resin).

Rabbits seem absolutely insusceptible to the action of cannabis.

Therapeutic Uses.— Cannabis is a rather unsafe and uncertain hypnotic. Its use is not advisable. The extract is added to corn-remedies, mainly on account of its bright-green color.

Cannabis Indica (U. S. P., B. P.).—*Indian Hemp* (Hashish, Bhang, Ganja, Charas, Momeka, etc.).— The flowering tops of the female plant of *Cannabis sativa,* Urticaceæ. Collected in India.

Botanically, the plant is identical with that grown in the temperate zone, but the action is only developed in certain regions; in India itself only the plants growing above a level of 6,000 to 8,000 feet exude the resin "charas," which is considered the most valuable.

It was used in China as a medicine as early as the fifth century B. C., but the Greeks and Romans were probably not acquainted with it. It is now used as an intoxicant in many Eastern countries.

The *active ingredient* is a resin, *cannabinol* (Fraenkel, 1903), $C_{21}H_{30}O_2$, which presents the appearance of a thick reddish yellow oil, soluble in petroleum ether, etc. (not identical with the commercial "cannabinol"). This changes by oxidation to an inactive black pitch. The change accounts for the deterioration which the drug and its preparations undergo in keeping. Cannabis also contains a volatile oil (terpenes), paraffin, pitch, etc., which are not concerned in its action. There is no specific alkaloid, but the extracts may give alkaloid reaction from the formation of cholin and triamethylamin. These are also not connected with the action. The fresh extract has a beautiful green color (if prepared without excessive heat), due to chlorophyl. The active principle is completely extracted by alcohol, but is insoluble in water. Hemp grown in Western countries is generally devoid of cannabinol, and is inactive.

Preparations (alcoholic; not miscible with water):

Extractum Cannabis Indicæ (U. S. P., B. P.)—*Dose:* 0.015 to 0.03. Gm. (¼ to ½ grain) (0.01 Gm. = ⅕ gr., U. S. P.).

Fluidextractum Cannabis Ind. (U. S. P.).—*Dose:* 0.06 to 0.6 c. c. (1 to 10 minims) (0.05 c. c. = 1 ♏, U. S. P.).

Tinctura Cannabis Indicæ, 10% (U. S. P., B. P.).—*Dose:* 1 to 2 c. c. (15 to 30 minims) (0.6 c. c. = 10 ♏, U. S P.).

Cannabin, an alkaloid; *Cannabinol,* an oil; *Cannabinon,* a resin, are

[1] Exercise 24. Dixon, 1899.

found on the market, and are claimed by their manufacturers to represent the active principles. They have not been subjected to sufficient scientific investigation.

Only such preparations should be employed as have been tested on dogs.

Hops are credited with some hypnotic power, but this is at best weak and uncertain. The somnifacient action of beer is certainly due mainly to the alcohol, although the hops may contribute to it. The old beers were brewed without this addition. The first notice of such use occurs in 1050, but it was legally prohibited in England as late as 1530. At present the difficulty lies the other way, brewers sometimes adding other bitter substances — even strychnin and picrotoxin have been reported.

Humulus (U. S. P.) [**Lupulus**, B. P.]. *Hops.*— The dried strobiles (female flowers) of *Humulus Lupulus*, Urticaceæ. Cultivated. The active part consists in small glands, which can be separated as a powder:

Lupulinum (U. S. P., B. P.).—*Lupulin.*— Volatile oil, cholin, resin; active principle not determined.

Two acids (and *αβ lupulinic acids*) are present. They stimulate the respiratory and vagus centers; this is followed by depression. They also depress the cardiac muscle. Lupulin contains a further, unknown, constituent which is insoluble in water and a strong cardiac poison. All these, however, are not active when administered by the stomach, and are therefore not concerned in the action of the drug.
Dose: 0.2 to 1 Gm. (3 to 15 grs.) (0.5 Gm. = 7½ grs., U. S. P.).
Preparations: U. S. P.: (These are not miscible with water.)
Fluidextractum Lupulini.— Alcohol. *Dose:* 0.5 c. c. = 8 ♏.
Oleoresina Lupulini.— Acetone. *Dose:* 0.2 Gm. = 3 grs.
B. P.:
Tinctura Lupuli.— 20%; one-half alcohol. *Dose:* 8 to 30 c. c. (2 to 8 drachms).
Infusum Lupuli.— *Dose:* 30 to 60 c. c. (1 to 2 ozs.).

Lactucarium (U. S. P.).— *Lettuce-juice.*— The dried milky juice from the stalks of the Lettuce, *Lactuca virosa*, Compositæ. Cultivated.

Resin, gum; nature of active principle not determined. The presence of atropin was claimed, but later investigations have proven this erroneous. Lettuce leaves and lactucarium are credited with some hypnotic power, but the remedy is obsolete.
Dose: 0.6 to 4 Gm. (10 to 60 grs.).
Preparations:
Syrupus Lactucarii (U. S. P.).— 5%. *Dose:* 8 c. c = 2ʒ.
Tinctura Lactucarii (U. S. P.).— 50%. Dil. alcohol and glycerin. *Dose:* 2 c. c. = 30 ♏.

Related to the stimulating action of cannabis are certain products obtained by the Mexican Indians from the juices of various cacti, generally by fermentation. The most interesting of these is the **mescal**, prepared from Anhalonium Lewinii. This contains four alkaloids which agree qualitatively in their actions. The latter are quite numerous: a slowing of the heart, a curare action on striped muscles, a specific depression of the respiratory center, and a stimulation of other parts of the central nervous system. The stimulation is shown mainly in certain special senses, most conspicuously in vision, the effect appearing as a loss of coordination. It produces hallucination of all the special senses, but particularly of sight. There are flashes and lines of ever-changing colors. Since they are the same in both eyes, they must be central (Dixon, 1899).

Study Materia Medica Lesson 20.

The drug is not at all used therapeutically, although the euthanasia which it produces even in small doses, and the cardiac depression without a constriction of the vessels, might possibly be useful.

The Mexican drink "**pulque,**" produced by the fermentation of the juice of the maguey plant, produces an alcoholic intoxication modified by the presence of other substances, perhaps belonging to this group. In the intoxication, the thought and language are low, the patient is boisterous and quarrelsome, and, it is said, generally unhappy.

Loco Disease.— Horses, cattle, and sheep on the Western stock ranches are subject to this peculiar disease, which bears some resemblance to drug-habits. There is no agreement as to the cause of this condition. Marshall (1904) attributes it to bad feeding, parasites, etc. The more prevalent opinion, however, refers it to the eating a number of leguminous plants (loco weeds — especially Aragallus spicatus). The poisoning may be acute or chronic, *i. e.*, death may result in a few days, or the disease may persist for years. The chronic form is due to an acquired tolerance, the animals developing a craving for the plant, a regular drug habit. "The sheep may be seen hurrying with trembling gait from one low plant to another, devouring each with nervous haste." Normal animals avoid the plant, but may be induced to eat it by the example of others. The eating of alkali also seems to pervert the appetite and to favor the acquirement of the habit.

The symptoms consist in motor incoordination, forced movements, misjudgment of distance, stupidity, apparently hallucinations. In the the chronic form there is emaciation. Death is preceded by coma and convulsions. When extracts are administered to rabbits, the effects are mainly narcotic. The active principle is said to be an acid.

The symptoms consist in motor incoordination, forced movements. pletely if the drug is withheld, although horses preserve some nervous disorder permanently. No withdrawal symptoms appear to exist. All the animals will recur to the habit if the opportunity is given.

C. HYDRASTIS.

Hydrastis (Golden Seal) contains at least three alkaloids: Hydrastin, Berberin and Canadin. The actions are due mainly to hydrastin. *Berberin*[1] acts as a simple bitter in small doses. Large doses cause a fall of blood-pressure from vasomotor paralysis. This, as also its bitter taste and the yellow stain which it produces on linen, render it objectionable in the therapeutic use of hydrastis. *Canadin* resembles morphin somewhat in its action. It is present in too small a quantity to be of practical importance.

Hydrastin is very closely allied to narcotin in its composition and actions. The two alkaloids also yield analogous decomposition products:

Hydrastin $= C_{19}H_{14}NO_4.H.2OCH_3$.
Narcotin $= C_{19}H_{14}NO_4.3OCH_3$.

$$\left.\begin{array}{l} C_{21}H_{21}NO_4 + O \\ \text{Hydrastin.} \\ C_{22}H_{23}NO_7 + 2O \\ \text{Narcotin.} \end{array}\right\} \begin{array}{c} = C_{10}H_{10}O_5 \\ \\ \text{Opianic Acid.} \end{array} + \left\{\begin{array}{l} C_{11}H_{11}NO_2 \\ \text{Hydrastinin.} \\ C_{12}H_{13}NO_4 \\ \text{Cotarnin.} \end{array}\right.$$

Actions of Hydrastin and Hydrastis.— *Moderate doses* produce a strychnin effect on the spinal cord, the paralytic phase being quite prominent. There is no narcosis. Hydrastin is allied to the protopin group (see page 191), in that it has a weak local anesthetic action, and in producing a paralysis of the cardiac and skeletal muscles. *Large doses* produce a fall of blood-pressure through central vagus stimulation, and vasomotor and cardiac paralysis.' Therapeutic doses produce a rise of *blood pressure,* but the statements of different investigators are quite contradictory as to the importance of this effect: Some claim that the rise is large and persistent; others that it is small and short. Some insist on a direct stimulation of the cardiac and arterial muscle, whilst others refer the effects to the strychnin action. It is not unlikely that the uncertain results are due to the presence of decomposition products. With so much variability in the effects, it seems only safe to conclude that *the rise of blood pressure is uncertain, and usually small and short,* and that it is soon followed by a fall, due to vasodilatation and cardiac depression ('Marfori, 1890).

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[1] Berberin is an intensely yellow alkaloid found in many plants, especially in Berberis vulgaris, Xanthoxylon, Coptis, Sanguinaria, Podophyllum, etc.

Therapeutic Uses.— Hydrastis has been used internally as a *stomachic* (due to the berberin); in epilepsy (empiric); and *to check internal hemorrhage.* This last use is based on the supposed vasoconstriction. *Locally* it is used especially on the genito-urinary tract, in *catarrhal conditions* and hemorrhage. The therapeutic uses of hydrastis are not endorsed by experimental data, and the clinical evidence appears insufficient to establish their value.

Hydrastinin.— Hydrastin splits by hydration into opianic acid, and a new alkaloid, hydrastinin, the actions of which differ radically from those of its mother-substance. It has lost the spinal actions and the paralytic effects on muscle. These are replaced by a direct stimulation of cardiac and arterial muscle, and by a stimulation of the medulla. This is succeeded by paralysis, death occurring through stoppage of the respiration.

The most conspicuous effect of moderate doses is a *marked and persistent rise of blood pressure,* due to the stimulation of the vasomotor center, and of the cardiac and arterial muscle. (The kidney vessels, however, are dilated. Paldrock, 1896.) This pressure effect is not followed by a compensating fall, so that hydrastinin should be an ideal drug for raising the blood pressure (in shock, hemorrhage, etc.). It has not, however, been tried sufficiently to decide on its value.

Cotarnin.— Narcotin also splits by hydration into opianic acid, and cotarnin (trade name: *stypticin*). This retains the narcotic action of narcotin, but has lost the strychnin-effect. It has been recommended against *hemorrhage,* and good results are claimed for it. No satisfactory explanation is offered except that it lowers the blood-pressure through vasomotor depression. It is also said to start uterine contraction. More extensive experience is needed before the value of this drug can be considered as proven.

Hydrastis (U. S. P.) [**Hydrastis Rhizoma,** B. P.].—The rhizome and roots of *Hydrastis canadenis*, Ranunculaceæ. North America.

Berberin, 3 to 4%; hydrastin, at least 2.5%, U. S. P.; canadin; resin.

Preparations:

Fluidextractum Hydrastis (U. S. P.) [*Ex. H. Liquidum*, B. P.].—Six-tenths alcohol, one-tenth glycerin. Miscible with water or alcohol. 2% hydrastin. *Dose:* 2 to 8 c. c. (½ to 2 drachms) (2 c. c. = 30 ♏., U. S. P.).

Glyceritum Hydrastis (U. S. P.).—A fluid extract having equal volumes of glycerin and water as menstruum. Useful as injection. Miscible with water or alcohol. *Dose:* 2 to 8 c. c. (½ to 2 drachms) (2 c. c. = 30 ♏., U. S. P.).

Tinctura Hydrastis (U. S. P., B. P.).—20%; 0.4% hydrastin, one-half alcohol. *Dose:* 8 to 20 c. c. (2 to 5 drachms) (4 c. c. = 13. U. S. P.).

Hydrastina (U. S. P.), $C_{21}H_{21}NO_6$.—Insoluble in water, soluble in 135 alcohol. Not employed externally on account of its insolubility. *Dose:* 0.010 to 0.03 Gm. (⅕ to ½ grain) (10 mg. = ⅕ gr., U. S. P.).

Hydrastininæ Hydrochloridum (U. S.P.), $C_{11}H_{11}NO_2.HCl$.—Prepared by the oxidation of hydrastin with nitric acid. Soluble in 0.3 water or 3 alcohol. *Dose:* 30 mg. = ½ gr. Hypodermically in 10% solution.

* *Cotarninæ Hydrochloridum* (Stypticin).—Yellow powder, soluble in water or alcohol. *Dose:* 0.01 to 0.3 Gm. (1½ to 4 grs.) by mouth, or in 10% injection.

CHAPTER X.

COCAIN GROUP.

I. DERIVATION.

Cocain is derived from the leaves of Erythroxylon Coca, a tree indigenous to South America. The leaves were chewed from time immemorial by the natives to relieve fatigue and hunger, and also to produce psychic stimulation somewhat after the manner of caffein. It is now cultivated in some other tropical countries.

On the first introduction of the leaves into Europe the effects were disappointing, and the statements of the explorers were regarded as travelers' tales. These disappointing results were due to the fact that the sensations for which it is employed by the natives — hunger and fatigue — did not exist in the experimenters. The drug then fell very largely into disuse.

The discoverer of cocain (Niemann, 1860) and several others had observed the anesthetic action of the tongue, but this did not attract the attention of medical men, perhaps because the observers were mainly chemists. The first classical pharmacologic work on the drug was done by von Anrep (1880). The introduction of cocain as a practical local anesthetic is mainly due to Koller (1884).

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* **Not official.**

Study Materia Medica Lesson 20.

The principal action of cocain — the local anesthesia — is also possessed by a number of other drugs; but since these differ considerably in other respects, their actions will be described separately.

II. SUMMARY OF ACTIONS.

1. Cocain is a strong *general protoplasmic poison,* paralyzing all cells with which it is placed in contact. However, it acts more strongly on some than on others.

2. Its local application paralyzes nerve cells, fibers and endings. Sensory nerves are the most sensitive; so that cocain acts as a *local anesthetic.* The structures generally recover completely when the cocain is removed.

3. It produces a *local vasoconstriction* at the place of application.

4. It dilates the pupil, both with direct and systemic administration, by sympathetic stimulation, central and peripheral.

5. On *systemic administration* it causes an irregular, but on the whole a descending, stimulation and paralysis of the entire *central nervous system.*

6. It produces a specific *risc of temperature,* by stimulating the thermogenetic center of the caudate nuclei.

7. It causes a *vacuolar degeneration of the liver cells* in rabbits.

8. Its continued use leads to the formation of a *habit* resembling morphinism.

III. DETAILS OF ACTION.

The systemic effects of cocain are rather variable and complex, depending largely upon the dose. Whilst all structures are first stimulated and then paralyzed, the susceptibility to the poison is not uniform. Indeed, some portions of the nervous system show only stimulation, death occurring before the paralysis of these structures is reached. On this account also, the peripheral actions are only produced by local application.

Central Nervous System.—(*a*) The *frog* shows at first symptoms of stimulation by increase of the voluntary movements and exaggeration of the reflexes, sometimes leading to convulsions. This is followed by paralysis of the whole central nervous system.

(*b*) The symptoms in *mammals* resemble at once those of poisoning by atropin, morphin, and caffein.

(A) Brain.— The first effect is a well-marked stimulation of the higher parts of the brain (caffein action). This is shown in animals by increased movement, which is perfectly normal in character. In man there is a certain amount of *psychic stimulation* and also wakefulness. A greater *endurance against fatigue and hunger* is also noticed.

How far this may be due to a stimulation after the manner of caffein, or to a narcosis, after the manner of morphin, is impossible to state. It is not at all unlikely that both play a part. In regard to the sensation of hunger, it is also probable that local anesthetization of the stomach aids in the effect.

The resistance to fatigue can be demonstrated with the ergograph.

Another evidence of the stimulating action of cocain is furnished by the fact that animals to which it has been administered are more difficult to put and to keep under chloroform or other anesthesia. The stimulation is greatest with excitable individuals, and may seriously interfere with operations.

This stage of stimulation may be very short or even absent. With somewhat larger doses it may be followed by depression, first of the *coordinating functions.* The movements lose their purposive type and become choreic. There is then a general *narcosis* after the manner of morphin.

This is followed by *convulsions.*

The seat of these has not been exactly determined. They, like the other effects, are probably descending, and the different convulsive centers may be affected in succession. In some stages at least they seem to reside exclusively in the hind brain.

If the paralysis is rapid, the convulsive stage may not appear.

The *thermogenetic center* is stimulated, so that there is a rise of temperature.

The thermal action of cocain is exerted upon heat production, for it is not effective after curare (which cuts down heat production by preventing muscular movement). The heat dissipation is a trifle increased as an indirect consequence, *i. e.*, through the rise of temperature. The increased heat-production is not due to the convulsions, for it occurs in the absence of the latter (nevertheless, when they exist, they contribute to the thermal action, as do also the psychical and cerebromotor excitement). The cocain must therefore produce its action directly on a thermogenetic center (Reickert, 1902).

The following centers are generally accepted by physiologists as regulating heat production: (1) A general or reflex thermogenetic center in the spinal cord, which acts on the muscles through specific nerve fibers, and which is able to keep up the normal heat production for some hours even in the absence of the higher centers. The latter act through the spinal center. (2) A thermoaccelerator center in the caudate nucleus, and (3) another in the pontobulbar region: these differ somewhat in their functions. (4) A thermoinhibitory center in the (crucial) cerebral cortex.

These centers regulate the specific heat production, which has its seat mainly in the muscles. A large amount of heat is also generated in the body incidental to the normal physiologic activity of the muscles, etc. The specific heat production varies normally in inverse ratio to the incidental generation of heat, so that the total heat production is kept nearly constant. The action of *cocain* is not upon the cord, nor on the pontobulbar centers, for it does not occur on section of the crura cerebri. Nor does it act on the crucial centers, for it is effective after the abiation of these. Its action consists, therefore, in a *stimulation of the caudate nuclei;* a conclusion which is confirmed by their extirpation: as long as any of the nuclear substance remains, cocain produces its effect, but it has no result if the excision is complete.

(**B**) The **medulla** is affected at quite an early stage. The *respiration* is at first accelerated. During the spasms it is irregular. The volume then diminishes. It may assume the Cheyne-Stokes type. Respiratory paralysis is the usual *cause of death.*

This is also the first center to fail when the cocain is applied locally to the fourth ventricle.

The *vasomotor center* presents an early stimulation and much later paralysis. The changes in this center account for the variation in the quantity of urine, which may be increased, but is more often diminished.

The *vagus center* is first stimulated, but suffers depression quite early.

The effects on the general circulation are partly central, partly peripheral. They vary according to the dose, as shown diagramatically in Fig. 54.

The effects also vary somewhat with different individuals, as some are much more susceptible to small doses, or to certain phases of the action. The typical actions are briefly as follows:

Very small doses diminish the pulse rate, by stimulation of the vagus center. There is a quick rise of *blood pressure* from stimulation of the vasomotor center; this is followed by a temporary fall due to the slowing.

Moderate doses quicken the pulse, mainly by central and peripheral depression of the vagus, with some stimulation of the accelerator center. *The pressure rises,* from stimulation of the vasomotor center, aided by the faster heart rate. It occurs also in the absence of convulsions.

Large doses cause a great fall of pressure and slow and weak pulse, from the depression of the medullary centers (collapse) and of the cardiac muscle.

The *effect on the heart-rate* demands some further discussion: The *slowing* from small doses does not occur if the vagi have been cut, so that it is of central origin. The *quickening* from moderate doses is also less marked if the vagi have been divided, so that it is probably due in part to a depression of the vagus center. The vagus ganglia are also depressed, for electrical stimulation of the vagus trunk is only partly successful. In the frog these ganglia can be paralyzed completely by the local application of cocain, but in the intact mammal the paralysis is not complete. Some quickening occurs, however, even when the vagi have been divided, but none is seen if the accelerators have also been cut. The excised heart (Hedbom-Langendorff method) shows a lessening of both rate and systole. This justifies the conclusion that there must also be a stimulation of the accelerator center. The *final slowing* is due to a direct paralysis of the muscle, for it is accompanied by weakening of the contraction, and it occurs after atropin, and in the excised heart. The intravenous injection of cocain has a very pronounced effect on the *splanchnic circulation.* The intestines appear unusually pale. Handling of the viscera and other measures of "shock" which cause a splanchnic dilation and consequent fall of blood-pressure in normal animals, have less or no effect after cocain. Burning and stimulation of the sciatic, which cause a rise of pressure normally, are also ineffective. It has not been investigated whether this want of response is due to a blocking of afferent impulses; to a peculiar condition of the vasomotor center; or to a blocking of the splanchic (Crile, 1901).

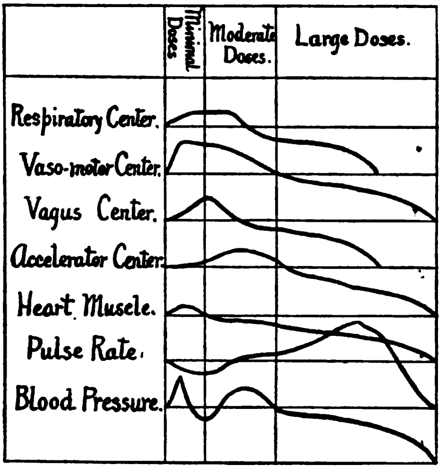

Fig. 54.—*Diagram of the Actions of Cocain on Respiration and Circulation.* (A rise of the curve signifies an increase or stimulation; a fall, the reverse.)

The **vomiting** which frequently occurs in cocain poisoning is perhaps due to the medullary stimulation, but its mechanism has not been fully investigated.

(C) **Spinal Cord.**— In frogs in which the brain has been removed, cocain causes at first an increase of the reflexes, then convulsions, and finally total paralysis. In intact animals this effect is obscured by the action on the higher centers of the nervous system.

The results of applying cocain directly to the cord will be considered later.

Effect on Metabolism.— In rabbits, large doses of cocain cause rapid loss of weight. The quantity of urine, its specific gravity, and particularly the urea, are diminished, whilst the incompletely oxidized (extractive) nitrogen is increased. During recovery, the quantity of urine returns promptly to normal or above; the disturbances of the nitrogen metabolism persist for some time (Maestro, 1904).

THE LOCAL ACTION OF COCAIN.[1]

(A) When cocain is brought into contact with the **nerve endings,** it paralyzes them in certain situations. In the skin it affects those having to do with pain and touch, but in a lesser degree or not at all, those having to do with temperature. In the nose it abolishes the sense of odor; in the tongue, the taste, especially for bitter, less for sweet and sour substances; it has no effect on salty taste.

Like quite a number of other poisons,— ether, alcohol, chloroform, carbolic acid, etc.,— it produces a *temporary paralysis of the nerve-trunk* to which it is directly applied.

If fairly strong solutions are used, the paralysis is as complete as if the nerve were divided with a knife, and it can be produced on all kinds of nerves. If the solution is washed away the nerve soon recovers its functions completely. Very strong solution can produce neuritis and permanent paralysis. With solutions weaker than ½% the paralysis is incomplete; ganglia are paralyzed most readily, then sensory fibers, the motor fibers being the most resistant.

This selective paralysis is also seen in other fibers: when applied to the appropriate mixed nerves, the centripetal vagus fibres are paralyzed before the centrifugal; the vasoconstrictors before the vasodilators; the bronchial constrictors before the dilators; etc. (Dixon, 1904). The cocainization of the vagus has been suggested in cases of vagus cardiac standstill during operation.

The injection of cocain into the *spinal subdural canal* acts in the same manner, *i. e.,* by paralyzing the sensory fibers of the nerve roots. In this way a complete anesthesia to pain, less to touch, may be produced. The motor nerves are but slightly interfered with, while consciousness remains normal.

When cocain is applied to a mucous membrane, it renders it *anemic.* This is probably due to a local stimulating action on the arterial walls, although the cause is not certain. This effect, as well as the toxic action on protoplasm, produces an astringent sensation and an actual contraction of vascular formations, such as polypi.[1]

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[1] Exercise 43.

In all these sensory effects there is no stimulation, such as would be evinced by pain, etc.

It is claimed that cocain produces certain *histologic changes* in the sensory corpuscles of Herbst and Vater-Pacini. None have as yet been demonstrated in nerve trunks or the spinal cord after the injection of cocain, but the methods were perhaps not sufficiently delicate.

With the application of 2% to 10% solution to the mucous membranes, the anesthesia appears in a few minutes and lasts ten to thirty minutes.

Very large doses also paralyze the motor endings in frogs.

(B) **Action of Cocain on the Eye.**[2]— When cocain is administered either locally to the eye or systemically, there is usually a submaximal dilation of the pupil. The iris, however, still reacts to light. The accommodation is also impaired so that the punctum proximum is more distant.

The mydriasis differs from that produced by atropin, in the persistence of the reaction to light, and the dilatation is less complete. It also differs in several other respects: Pilocarpin and muscarin produce constriction easily after cocain, but not so readily after atropin. Cocain also produces a contraction of the vessels of the iris. The eyelids stand wide open: there is exophthalmos. The intraocular tension is reduced. These phenomena correspond exactly to those produced by the stimulation of the cervical sympathetic.

When the sympathetic fibers have degenerated (eight days after extirpation of the superior cervical ganglia) the cocain is inactive to the eye. Its effects must, therefore, be due to stimulation of the sympathetic, and since they do not disappear immediately after section of this nerve, but only after it has become degenerated, this stimulation must reside, at least in part, in the endings. But since it is then much weaker, it must be in part central (Schultz).

The atropin dilatation is caused by paralysis of the oculomotor endings. This plays no part in the cocain action except with very strong solutions, for stimulation of the oculomotor trunk still causes contraction.

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[1] It is claimed that in the frog it dilates the vessels on local application.

[2] Consult Exercise 54.

In birds' eyes cocain produces no dilatation, whereas in frogs it is very marked.

In addition to the mydriasis, it of course also produces anesthesia and destruction of reflexes, such as winking, when locally applied.

Cocain sometimes produces cloudiness and even gangrene of the cornea, due to its protoplasmic toxicity and to the drying, etc., resulting from the abolition of the reflexes.

The hypodermic injection may also lead to abscess formation.

Cocain has practically no effect on *secretion*, nor has it any action on *metabolism* beyond the increase of temperature, which has already been noted.

It is toxic to the lower forms of animal life (infusoria, etc.), but scarcely to bacteria.

Fate.— The cocain is almost completely destroyed in the organism of mammals, not even ecgonin is found in the urine. Outside of the body, it is *readily decomposed* by heating into benzoic acid and *ecgonin.*

This occurs if solutions are heated for some time above 80° C. (176° F.). Cocain solutions cannot, therefore, be sterilized by boiling, but the object may be effected by bringing the solution repeatedly to 80° C. and cooling between.

IV. TOXICOLOGY.

This is of special importance, since cocain poisoning is not a very uncommon occurrence in the therapeutic employment of the drug. Very large amounts are sometimes used in a most careless manner for local anesthesia, and since the absorption is fairly rapid, serious and even fatal results may follow. The uncertainty of the absorption accounts in part for the varying intensity of the effects. In some cases 2 drops of a 4% solution (=0.005 Gms.) in the conjunctival sac caused serious collapse; whilst very much larger doses produced no effect in other cases. The ordinary *fatal dose* lies about 0.2 Gm. (3 grains). The smallest quantity which has proved fatal is 0.08 Gm.

The *symptoms* of acute cocain poisoning are somewhat variable. There may be excitement followed by depression and melancholia, or the former may be absent. When the drug is taken by the mouth, there is often the sensation of pricking of the tongue, nausea, vomiting, abdominal pain, etc.

The pupils are dilated and the accommodation impaired. The heart is quickened and shows palpitation; the respiration is accelerated and deepened, and later shallow and irregular and then Cheyne-Stokes; the skin is pale and cyanotic and often exhibits the sensation of formication. There is a feeling of faintness, vertigo, flickering before the eyes, then coma. The reflexes are heightened and may pass into choreic movements or general convulsions. This is followed by collapse. The cause of death is respiratory failure. The postmortem appearances are those of asphyxia.

The *treatment* consists in evacuation of the stomach and chemic antidotes if the drug has been taken by the mouth; otherwise, of the collapse treatment: Strychnin, caffein, ammonium carbonate, sinapism to the chest and abdomen. The head should be lowered. During the convulsions, chloroform and artificial respiration. Amyl nitrite is recommended.

Chronic Cocain-poisoning.— The effects of the cocain habit are essentially the same as those of opiumism, but may usually be differentiated by the fact that cocain produces mania, epileptiform convulsions, and dilatation of the pupils. The psychic functions suffer even more severely than in morphinism. There are insomnia, hallucinations, apathy, and melancholia. In addition, it produces marked digestive disturbance, hunger alternating with thirst, and constipation. After this, marasmus, debility, emaciation, anemia, edema, and ascites.

On withdrawal it presents abstinence symptoms similar to those of morphin, but not quite so violent. Cocain was at one time used for breaking up the morphin habit, but it should not be thus employed, since the cocain-habit is the more dangerous.

The abuse of cocain is unfortunately greatly on the increase, especially amongst negroes and the lower classes. The habit develops more rapidly than morphinism, and is more difficult to cure. A tolerance is acquired, and it is said that as much as 3 Gms. per day are sometimes taken.

V. THERAPEUTICS.

1. **Central Nervous System.**— As a brain stimulant, against fatigue, and as a general tonic, it has no advantages and many disadvantages as compared with other substances, especially caffein and strychnin.

2. Its main use is for the **production of local anesthesia,**

especially in minor operations. The cocain abolishes the sensation of pain more or less completely in about five minutes, the anesthesia lasting for about half an hour. Solutions of 2 to 5% are applied to the surface of mucous membranes, or injected under the skin. Stronger solutions are dangerous and offer no advantage. Application to the surface of the skin is useless, since the drug is not absorbed by this channel. Mucous surfaces, on the other hand, absorb it readily. The local action ceases, and the undesired systemic action appears, as the alkaloid is absorbed into the circulation. It is therefore desirable to limit the local circulation, *e. g.*, by a constricting rubber band. The vasoconstrictor action of the cocain itself aids in lessening its absorption; this effect may be heightened by the addition of the suprarenal alkaloid (1:10000 to 1:100000).

In *eye* and *larynx operations* the abolition of reflexes and the diminution of hemorrhage are very useful side-actions. In connection with its action on the eye, it must be remembered that it does not anesthetize the iris when applied to the cornea.

Cocain is also very useful in the treatment of diseases which appear to be due to heightened irritability of the peripheral endings, such as *hay-fever* and *asthma*. In these the cocainization of the nasal mucous membrane is often specific. The astringent action renders it very effective in acute coryza. The danger of the formation of the habit very often interferes with its use.

One per cent. cocain ointment has been recommended in herpes zoster; it is said to not only relieve the pain, but to put a stop to the disease.

Cocain is also useful locally in *hemorrhoids*, producing contraction and diminishing pain. It has been taken by the stomach to prevent *vomiting* and dyspeptic pain.

3. For the use of cocain in **larger operations** a number of methods have been proposed.

The *infiltration method of Schleich* consists in the injection of very dilute solutions ($^1/_{100}$ to $1/5$%), under considerable pressure, into the very place where the incision is to be made.

The object is to produce a local edema, which supports the action of the cocain by causing local anemia and by compressing the nerve filaments. The injections can be made with an antitoxin syringe with a long needle, by means of which the solution is first injected into (not under) the epidermis, so as to raise a blister. The needle being left in place and gradually pushed deeper, the entire field of operation is saturated with the solution, 30 to 500 c.c. being used. The solutions contain:

	I.	II.	III.
Cocain (or eucain, etc.)	0.2	0.1	0.01
Morphin	0.025	0.025	0.005
NaCl	0.2	0.2	0.2
5% Carbolic acid	5 drops per 100 c.c.	same	same
Aqua destillata ad	100	100	100

The morphin may be omitted.

II. is the most generally useful; III. is employed where much solution is required; and I. in the presence of acute inflammation.

In the *paraneural method* the solution, of a strength of ½ to 2%, is injected in the neighborhood of the nerve trunk. The results are uncertain, and inferior to those of the *intraneural method*. In this, similar solutions are injected directly into the nerve trunk. If the injection is made quickly and directly into the nerve tissue, the procedure is quite painful. A few drops should first be injected under the nerve sheath. When these have caused a local anesthesia, the needle should be pushed deeper and more of the solution injected, until the anesthesia is complete. In this way the pain is very slight.

A combination of all the above methods is most useful. The skin and superficial muscles are anesthetized by infiltration. The deeper structures are exposed, and the smaller nerves are treated by the para-, the larger by the intraneural methods.[1] The *complete* blocking of nerve impulses obtained in this way prevents surgical shock. No method of local anesthesia can, however, prevent the psychic shock and pain, the nervous dread of the patient, the removal of which is one of the most valuable features of general anesthesia; but it may at least be lessened by morphin (0.015 Gm. hypodermically) half an hour before the operation. It may at times be justifiable to operate without the knowledge of the patient, which is quite feasible by the use of cocain.

The *subdural method* is carried out by performing lumbar puncture, withdrawing a little cerebro-spinal fluid, and injecting ½ to 1 c.c. of a 2% solution of cocain (or eucain, etc.). The method was tried quite extensively, and is certainly efficient in producing a general anesthesia without loss of consciousness or motor power. A considerable number of accidents have, however, led to its abandonment. These are due to the direct conduction of the cocain to the floor of the fourth ventricle, where it leads to an immediate stoppage of respiration. The addition of adrenalin is said to lessen this danger.

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[1] By the careful use of this method, a surgeon performed a painless operation at the shoulder joint with 0.008 Gms. of Cocain.

Contra Indications to Cocain.— These consist in the danger of forming the habit; in the occasional acutely fatal action; and in unpleasant side-effects.

The toxic action is especially important, since very small doses are dangerous in susceptible individuals. The surgeon should remember that he is dealing with a very active poison, and should employ as small a quantity as possible. The limit of safety (even with local use) may be placed about 0.07 Gm. (1 grain); and 0.10 Gm. (1½ grains) should *never* be exceeded, under any circumstances.

The unpleasant side-effects consist in palpitation, nausea, and vomiting, headache, and insomnia.

VI. MATERIA MEDICA.

Coca (U. S. P., B. P.).—The leaves of *Erythroxylon Coca* (Huanuco Coca) or of *E. Truxillense* (Truxillo Coca), Erythroxylaceæ. Peru and Bolivia, cultivated. Cocain and similar alkaloids, at least 0.5%, U. S. P. Tannin.

Fluidextractum Cocæ (U. S. P.) [*Ext. C. Liqu., B. P.*].—0.5% alkaloids. *Dose:* 2 c. c. = 30 ♏.

Vinum Cocæ (U. S. P.).—6½%, with red wine. *Dose:* 16 c. c. = 4ʒ.

Cocaina (U. S. P., B. P.), $C_{17}H_{21}NO_4$.—Soluble in 600 water, 5 alcohol.

Cocainæ Hydrochloridum (U. S. P., B. P.), Coc.HCl.—Soluble in 0.4 water, 2.6 alcohol. Solutions cannot be sterilized by heat and deteriorate on keeping. They may be preserved fairly well by the addition of antiseptics, such as: salicylic acid, 0.15% (B. P.); or phenol, 0.015;% or saturated chloretone solution. *Dose:* 8 to 60 mg. (⅛ to 1 gr.) (30 mg. = ½ gr., U. S. P.). Hypodermically in 1 to 2% sol.; on mucous membranes, 1 to 10%; intraspinal, 15 mg. in 2%.

Oleatum Cocainæ (U. S. P.).—5%.

Lamellæ Cocainæ (B. P.).—Each 1/50 gr. of hydrochlorid.

Injectio Cocainæ Hypodermica (B. P.).—10%. *Dose:* 0.1 to 0.3 c. c. (2 to 5 minims).

Unguentum Cocainæ (B. P.).—4%.

Trochisci Krameriæ et Cocainæ (B. P.).—Each 1/20 grain.

VII. RELATION TO OTHER GROUPS.

The cocain group is very widely related: toxicity to protoplasm is common to all poisons; and many produce stimulation and depression of the central nervous system, and local anesthesia. A very close connection exists between cocain and atropin, chemically and in the central and peripheral actions. Cocain is an ether of ecgonin, which differs from tropin, the base of atropin, merely by the substitution in ecgonin of a COOH group, for an H of tropin.

VIII. COCAIN SUBSTITUTES.

The local anesthetic action of cocain leaves little to be desired, but several other features are very objectionable, as its high cost; the instability of the solutions, particularly on heating, and the consequent difficulty of sterilizing them; and the violent collapse action which is

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particularly dangerous on account of the idiosyncrasies. These objectionable features have led to the search for substitutes. Substances producing some degree of local anesthesia are by no means rare and have long been known. For instance, some of the other alkaloids of coca, yohimbin, atropin and its derivatives, aconitin, the coal-tar products generally, possess this action to some degree; but most of them are so inferior to cocain — either by weaker action, or by greater irritation or other undesired side-effects — that they can hardly be classed as competitors. Synthetic chemistry had to be invoked, and it has produced fairly satisfactory compounds. These are mostly built on the general chemical type of cocain.

The structure of cocain is quite well understood. It is a methyl-benzoyl-ester of *ecgonin*. Ecgonin itself produces only the least important of the actions of cocain, *viz.*, the hepatic degeneration. The other actions are only developed by the entrance of *both* radicles. The methyl may be replaced by any other alkyl radicle, without changing the actions of cocain. The benzoyl radicle, however, cannot be replaced by any other fatty or aromatic radicle without great impairment of the local anesthetic action. Indeed, the presence of the benzoyl group give the anesthetic properties to other alkaloids, and may be considered as the hook by which the molecule attaches itself to the protoplasm of the sensory cell. It is present in most of the cocain substitutes. The required conditions for the development of a local anesthetic action seem therefor to be: a base with a structure analogous to ecgonin, containing a benzoyl and an alkyl radicle in certain relations.

Comparative Value of Cocain and Its Substitutes.— It may be well to premise the detailed description of these substitutes, by some general statements concerning their value:

The valuable features of cocain consist in its strong, prompt and comparatively certain action; it is the best studied and the most familiar product of its class; the vasoconstriction lessens hemorrhage (but may be objectionable in snaring polypi); the dilation of the pupil may be a convenience in ophthalmic operations; it produces no local irritation; it acts through intact mucous membranes. Some of these features, viz., vasoconstrictor and mydriatic actions may be given to the substitutes by the addition of suprarenal alkaloid or atropin.

The *substitutes improve on cocain* mainly by their lesser toxicity (except holocain); by not injuring the cornea (except nirvanin and acoin); in being stable, sterilizable and antiseptic. *Eucain β* perhaps combines the greatest number of advantages, but has not given results in any way superior to freshly made solutions of cocain in skillful hands. *Orthoform* holds a field of its own, when a prolonged action on large denuded surfaces (wounds, ulcers, etc.) is required. *Freezing* recommends itself for minor operations on areas to which cocain or its soluble substitutes are not readily applied. Irritants, baths, etc., are most useful for a partial anesthesia of large and deep areas.

DETAILED DESCRIPTION OF THE COCAIN SUBSTITUTES.

Tropacocain.—The benzoylester of pseudo-tropin; occurs naturally in the leaves of the Javanese coca. It differs from cocain by greater anesthetic power, lesser toxicity, and greater resistance to decomposition. It does not produce mydriasis or vasoconstriction.

Eucain (Beta-Eucain; Benzoyl-Vinyl-Diaceton-Alkamin, $C_{15}H_{21}NO_2.HCl$).[1]—This synthetic product has essentially the same actions as cocain. The *peripheral actions* are in general weaker and slower than those of cocain, so that it must be used in twice the strength. The pupils are not dilated, and the tissues are rendered hyperemic rather than anemic. As regards the central actions, the stimulation is more conspicuous than with cocain. In toxic doses, convulsions form a striking feature, whilst the heart is slowed through stimulation of the vagus center, and the blood pressure falls greatly by a direct depression of the cardiac muscle. However, eucain is only a third or fifth as toxic as cocain, and fatal poisoning is almost or quite unknown. The solutions do not deteriorate on heating or keeping. The *hydrochlorid* is soluble in 33 parts of water; the lactate in 4 parts. The eucain salts are white crystalline powders.

Alpha-Eucain ($C_{19}H_{27}NO_4.Cl$) causes considerable local irritation and pain, so that its use has been abandoned.

Orthoform (methyl ester of oxyamido benzoic acid, $C_6H_3.OH.NH_2.COOCH_3$) is mainly useful when a prolonged anesthetic action on open surfaces (wounds, ulcers, etc.) is desired. Its value depends on its very limited solubility, and consequent slow absorption. Since it is rapidly excreted, it is practically non-toxic.

On the other hand, its insolubility precludes its use in hypodermic injection. When it is artificially brought into solution and injected, it is no less dangerous than cocain and has no advantage. Like cocain, it does not penetrate the intact skin, nor even mucous membranes, so that its usefulness is limited to open surfaces. Here its action may be prolonged for days. It has, however, in some cases caused a necrosis. Another use has been to mix it with caustics to deaden the pain of the latter. It has also been employed internally in ulcers or carcinoma of the stomach.

It is applied locally as a dusting powder, or in 10 to 20% ointment. It is incompatible with many substances, *e. g.*, silver or bismuth compounds, but may be prescribed with mercury, copper, and carbolic acid. It forms a white, odorless, and tasteless powder, almost insoluble in water, soluble in alcohol or ether.

Orthoform hydrochlorid is soluble, but produces so much irritation that it cannot be used.

Anesthesin (Para amido benzoic acid ethyl ester) resembles orthoform and has been recommended as a substitute, being stronger and less irritant. There is, however, greater danger of systemic poisoning. Its *hydrochlorid* is soluble, and has been used for infiltration anesthesia (0.25%).

Stovain (Hydrochlorid of amylene α β.—Hydrochlorid of α dimethylamin β benzoyl pentonal); same anesthetic power as cocain, with lesser toxicity; not destroyed by heating solutions to 115° C. Dilates blood vessels; does not change the pupil; somewhat irritant; very soluble in water. *Dose,* locally as for cocain; internally, 2 mg. = 1/30 gr.

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[1] *Euphthalmin* is another derivative of this base. It possesses mydriatic, but no anesthetic properties; see Index.
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Nirvanin (the hydrochlorid of the methyl-ester of diethyl glycocoll-p. amido-o. oxybenzoic acid; $(C_2H_5)_2 = N - CH_2 - CO - NH - C_6H_3(OH)CO_2CH_3.HCl.$).

This can be sterilized and is itself antiseptic. Its toxicity is about a tenth of cocain. Applied directly to the heart it is somewhat paralyzing, like most coal-tar derivatives. It is much weaker than cocain, and cannot penetrate through intact mucous membranes. It is irritant to the conjunctiva and therefore objectionable in eye-practice. Its main use is in dentistry as 2 to 5% solution. It forms white crystals of a peculiar bitter, somewhat sharp taste; very soluble in water or alcohol.

Holocain ($C_6H_4OC_2H_5NH.C(CH_3) = N - C_6H_4.OC_2H_5.HCl$), a phenacetin derivative, obtained by the reaction of phenacetin and paraphenetidin, with elimination of water. It has been recommended for ophthalmologic practice, since it is at least as powerful as cocain and does not injure the cornea. It is strongly antiseptic and keeps well, but is more toxic than cocain. It is used in ½ to 1% solution; the anesthesia appears in less than half a minute and lasts from five to ten minutes if the application is repeated. It has no action on the pupil or blood vessels. It dissolves in 50 parts of water. It is incompatible with alkaloids and alkaloidal precipitants.

Acoin, a guanidin derivative, is objectionable on account of irritant qualities. Used as ⅓ to 1% solution.

Subcutin, a soluble coal-tar derivative, used so far especially in Schleich's infiltration method.

Chloretone (Anesone, Chloroform-Acetone) has a slight anesthetic action, and is at the same time antiseptic. It is employed in 2% solution.

Yohimbin ($C_{22}H_{32}N_2O_4.HCl$).— An alkaloid isolated by Spiegel (1896) from the bark of the Yohimbehe tree (family of Apocynaceæ), growing in German West Africa. The local application (1 to 2% solution) produces the same *anesthetic effect* as cocain, and is less toxic. The effect begins in 10 to 15 minutes and lasts ½ to 1¾ hours. The vessels are rather dilated, even when adrenalin is added. In the eye, the anesthesia occurs more promptly (½ to 1 minute, lasting 10 to 15 minutes). It should not be used in this organ since it causes considerable irritation, lasting 4 to 6 hours. The pupils are dilated, the mydriasis lasting some 24 hours. Accommodation is but little affected.

When it is given by the mouth or hypodermically in moderate doses, it produces a general *vaso-dilation* in the skin, mucous membranes, and particularly in the *sexual organs.* In consequence of the latter, and perhaps by a direct action of the spinal centers, it produces erection. It does not seem to stimulate the production of spermatozoa or sexual desire.

In consequence of this action on animals, the alkaloid has been used as an aphrodisiac in neuropathic impotence; apparently with fair success. The reports must be accepted with caution, considering the possibility of psychic suggestion. The effect in animals occurs immediately; that in man only after some four to six weeks. This makes it difficult to explain the clinical observations by the animal experiments.

The continued administration of the alkaloid is said to lead to no bad effects; however, the resemblance of its actions to those of cocain would suggest that it may perhaps create a habit. Ordinary doses produce a psychic excitement similar to that of cocain (this has been referred to dilation of the cerebral vessels). There is also some distention of the cerebral vessels and vertigo. Gastric disturbance has been noticed. The effects of larger doses also agree with those of cocain (see page 219). *Toxic doses* cause general stimulation and subsequent paralysis of the nervous centers, particularly in the medulla. Death occurs by respiratory paralysis.

The free alkaloid and the solutions of the hydrochlorid being unstable, the dry salt is marketed in the form of tablets, containing 5 mg. ($^1/_{12}$ grain); three tablets per day are the ordinary *dose.*

IX. OTHER MEASURES PRODUCING LOCAL ANESTHESIA.

Atropin somewhat resembles cocain in its action, but is not nearly so strong. On the other hand, it is more readily absorbed from the intact skin, and can be employed in liniments and plasters.

Aconite causes first irritation and then anesthesia of the sensory nerves without inflammation.

Local anesthetic action is possessed by quite a number of the *aromatic series.* One of the most important is *carbolic acid.* This produces a marked anesthesia even in quite dilute solutions. Its application is, however, often injurious, since it produces destruction of the skin, and it may be absorbed in sufficient quantity to cause toxic symptoms. It is sometimes used in *paracentesis,* by applying a drop of the concentrated liquefied phenol to the skin, for the double purpose of anesthetizing and disinfecting. All the bodies of this series show both actions. Acetanilid or antipyrin may both be used in wounds in the form of dusting-powder, but are weaker.

Mechanical Means.—(*a*) *Protracted tepid baths.* These are useful especially in inflammation and skin diseases.

(*b*) *Cold baths* or *freezing* produce, in addition, local anemia. The anesthesia in freezing is complete, but it has several disadvantages. It is preceded by severe pain, and is often followed by vesication and gangrene of the skin. The freezing may be done in emergency by the application of ice and salt mixture, but more conveniently by spraying the surface with an easily volatilizable substance such as ether, or especially ethyl chlorid.

Counterirritants all produce a depression of the nerves after their stimulation. Here belong menthol, camphor, turpentine, essential oils, chloroform, alcohol, etc. (See Chapter XXIX, E.)

X. DRUGS PARALYZING TASTE ORGANS.

Allied in this respect to cocain, there are a number of substances whose action is, however, confined to taste. (See p. 103.)

Gymnemic Acid (from *Gymnema sylvestris*).—Destroys bitter and sweet; not acid or salt.

Eriodictyon (U. S. P.).—*Yerba Santa.* The leaves of *E. glutinosum,* Hydrophyllaceæ. California. Destroys bitter taste; not sweet, salt, or acid.

Volatile oil, resin, glucosid, eriodictic acid, tannin.

Preparations:

Fluidextractum Eriodictyon (U. S. P.).—Alcohol four-fifths. Makes turbid mixture with water. *Dose:* 0.6 to 2 c. c. (10 to 30 minims.).

**Elixir Eriodictyon Aromaticum,* N. F.—*Elixir Corrigens.* 6%. *Dose:* ad libitum.

CHAPTER XI.

ATROPIN GROUP.

This starts in a number of groups whose action is mainly peripheral, exerted upon ganglia and endings of glands, and cardiac and unstriped muscle. They also act on the central nervous system.

I. MEMBERS.

The atropin group comprises a number of alkaloids of very similar composition. These alkaloids occur in a variety of plants belonging to the family Solanaceæ (which also includes tobacco, capsicum, potato, etc.). The alkaloids formerly received specific names according to the plants from which they were obtained. It is now acknowledged that the group comprises a number of alkaloids, but that each of these occurs in all the plants, although in variable proportions. They are ester-like combinations of one of two bases, *tropin* and *oscin* (scopolin), with aromatic acids, especially tropeic acid, which are substituted for an H of the OH contained in the molecule of the base. This substitution brings out the characteristic action, the tropin itself being almost inactive. The derivatives of tropin are called *tropeins;* those of oscin, *osceins*. The alkaloids may be classified as follows:

Atropin and Hyoscyamin ($C_{17}H_{23}NO_3$) are isomeric, atropin being optically inactive, whilst hyoscyamin turns the plane of polarized light to left. They are tropeic acid-tropins. (It is probable that atropin is a mixture of l. and d. Hyoscyamin.)

Atroscin and Scopolamin ($C_{17}H_{21}NO_4$) are isomeric tropeic acid oscins. Atroscin corresponds to atropin, being optically inactive; whilst scopolamin corresponds to hyoscyamin, being levogyrous. A mixture of these two alkaloids forms the commercial *hyoscin*.

It will be noticed that Atroscin corresponds to Atropin, Scopolamin to Hyoscyamin. Atropin and Atroscin are the more stable products: Alkalies and many other agents convert hyoscyamin into atropin, scopolamin into atroscin.

Belladonnin and Atropamin are isomeric alkaloids (belladonnic acid tropeins). Their formula differs from atropin by the absence of a molecule of H_2O. They are present in the plants in very small amount, and it is possible that they are only formed during the extraction. Several other tropeins have been prepared *synthetically: Homatropin* is oxytoluic acid-tropin; *Benzoyltropein* is benzoic acid-tropin. *Ptomatropin,* an unisolated ptomain of spoiled meat, simulates the action of atropin, but its composition is not known.

Derivation.— Alkaloids of this group are contained in the following plants: Atropa Belladonna; Datura Stramonium; Hyoscyamus niger; Duboisia myoporoides; Mandragora autumnalis; Scopola atropoides; and in other species of these plants. The Belladonna, Scopola, Stramonium and Hyoscyamus (henbane) are *official.*

Belladonna and Stramonium contain mainly atropin and hyoscyamin; one or the other alkaloid may predominate. The hyoscyamin is the most widely distributed of these alkaloids, and is especially abundant in young parts of the plants, whereas older parts contain more atropin. It appears therefore that the hyoscyamin is the original alkaloid, and that it is partly transformed into atropin in the plant itself, and also during extraction. These plants also contain small traces of scopolamin and atroscin, but the latter alkaloids are relatively more abundant in *Hyoscyamus* and *Scopola,* taking the principal part in the actions of these plants.

The first indubitable notice of belladonna occurs in 1504, but it then came quickly into use for poisoning and cosmetic purposes. The name Atropos, which Linné gave to the plant, is from the oldest of the Three Fates, who cuts the thread of life. Belladonna comes from the Italian, "handsome woman," as it was used to give luster to the eyes.

II. SUMMARY OF ACTIONS.

These differ only quantitatively in the different members of the group.

1. Excitation and then paralysis of certain parts of the central nervous system, particularly the cerebral and medullary centers.

2. Primary paralysis of certain peripheral nerve endings. The peripheral organs paralyzed are the nervous mechanisms of secretion, pupil and accommodation, and of unstriped muscle, especially intestinal and cardiac. In these respects it is the exact antagonist of muscarin.

3. Slight stimulation and subsequent paralysis of smooth and cardiac muscle and other cells.

4. On local application it paralyzes also the sensory nerve endings.

The following description applies to atropin. The other members of the group will be discussed later.

III. DETAILS OF ACTIONS.

1. Central Nervous System.—(A) Hemispheres.— These show exaltation, with a subsequent depression, especially of the psychic centers: Restlessness, vertigo, choreoid movements, incoherent and constant speaking, uncontrollable laughter, delirium, usually cheerful, hallucinations, usually unpleasant, and finally mania.

These symptoms somewhat resemble those of the excitement stage of alcohol, but from the general action of the poison, they are probably stimulant, whereas the actions of alcohol are depressant.

In the secondary *paralytic stage,* drowsiness, coma, and finally convulsions occur, the latter largely from asphyxia, but appearing even if artificial respiration is maintained.

Some other cerebral centers are also affected:

The *vision* is disturbed more than can be explained by loss of accommodation.

The *motor areas* in dogs are stated by some observers to be more excitable, but others deny this.

The action of atropin on the *respiration* varies with the dose. Moderate doses generally cause an increase of respiration. This effect (Fig. 55 *C*) occurs when the vagi have been cut; the drug must therefore stimulate the respiratory center directly. The increase of respiration is greater, however, if the vagi are intact. This shows that atropin paralyzes also the afferent endings of the vagi, which ordinarily slow the respiration by tonic impulses. Other effects of the atropin — the psychic actions, etc.— may also react on the respiration. *Larger doses* depress the respiratory center, producing a slowing, Cheyne-Stokes type (Fig. 52), and finally cessation. The stoppage of respiration is the usual *cause of death,* but comes on very late in the poisoning. If artificial respiration is maintained, the animal may recover from six times the ordinary fatal dose. The effects on the *circulation* will be described later.

(**B**) The effects on **medulla and spinal cord** are similar in kind to those of strychnin, but are weaker and come on much later in the course of the poisoning. They are therefore of comparatively little importance.

2. Peripheral Actions.— (A) Glands.[1]— Amongst the first symptoms of atropin-poisoning is dryness of the mouth, hoarseness, thirst, difficult articulation, and dysphagia. All these symptoms arise from the suppression of the secretions of the mouth. Atropin diminishes not only the saliva, but also mucus, sweat, and gastric juice (both quantity and acidity). It is doubtful whether it has any effect on ordinary pancreatic secretion, on milk, or on urine (MacCallum, 1905), or on bile. It arrests the increase of pancreatic secretion when produced by physostigmin, or pilocarpin, etc., but not produced by secretin or acids.[2]

The *mechanism of this action* can be best studied on the *submaxillary gland.* One can at once exclude any central paralysis, for electric stimulation of the chorda tympani has no effect. The paralyzing action is therefore peripheral, and could be on the ganglia, endings, or salivary cells. The former are excluded by the fact that stimulation of the nerves peripheral to the ganglia is also ineffectual. Further, nicotin (which stimulates ganglia) does not act after atropin. We can eliminate paralysis of the gland-cells,[1] for stimulation of the sympathetic is still effectual. By exclusion, it results that the action must be on the nerve endings.

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[1] Exercise 55.

[2] The pancreatic stimulants which are antagonized by atropin yield active juice, whereas those which are not affected by atropin require the addition of erepsin. Camus & Gley, 1905.

The chorda, besides secretory, also contains vasodilator fibers. The latter are not paralyzed, and stimulation causes an increased venous outflow from the glands. The atropin paralysis is therefore highly selective. This holds true of its action in other situations.

There is every reason to assume that the diminution of other secretions by atropin depends on the same mechanism, viz., paralysis of the nerve-endings. Ganglion cells and nerve fibers are scarcely affected, even by direct application.

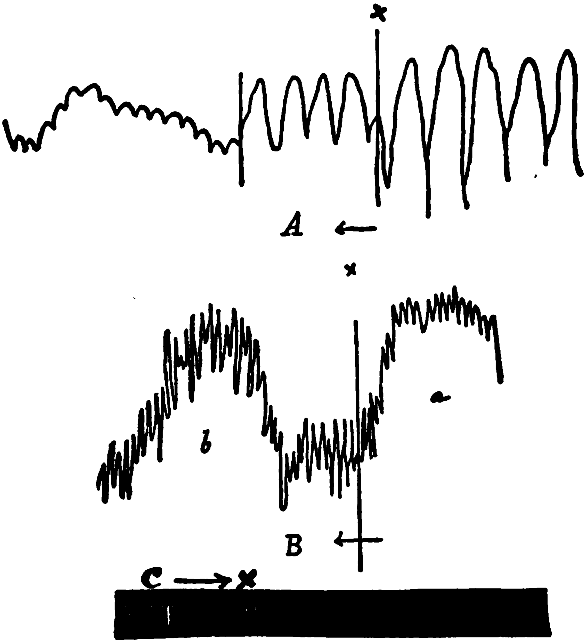

Fig. 55.— Atropin: action begins at ×. *A*, Carotid pressure, dog. Shows progressive quickening with smaller beats. *B*, Cardiomyogram, dog. The vagus ganglia were paralyzed by nicotin (*a*). The atropin causes strengthening of the beats. *C*, Respiration after atropin, intact rabbit.

Atropin produces entire suppression of the secretion of those glands (salivary and sweat), which normally act only in response to nervous excitation. With those glands which secrete independently of nervous impulses, the action of atropin is much less marked, and may be discoverable only when the glands are artificially stimulated. The alkaloid does not suppress *paralytic secretion;* nor any other secretion resulting from direct stimulation of gland cells.

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[1] This the theory generally held. Recent experiments go to show that atropin acts also on the cells, paralyzing the functions excited by the chorda, but not those under the control of the sympathetic.

The suppression of sweat causes a rise of *temperature* with *moderate doses,* notwithstanding the cutaneous vasodilatation. Animals which do not possess sweat glands (dog) do not show this rise. *Larger doses* produce a fall of temperature from a lessened heat production, the result of the general depression. The final convulsions may again cause a rise.

The nervous influences which cause the formation of sugar from glycogen in the liver are also cut off.

(B) In the eye[1] atropin causes dilatation of the pupil and loss of reaction to light; loss of the power of accommodation; and rise of intraocular pressure.

(*a*) To explain this action, it will be well to recapitulate the anatomic basis of the *pupillary mechanism* (Fig. 56):

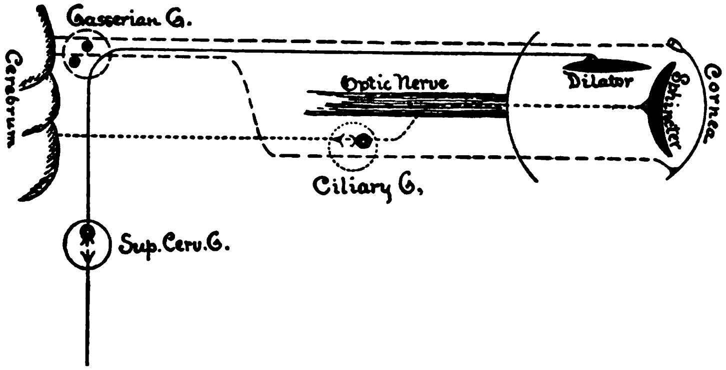

Fig. 56.—Innervation of iris (adapted from P. Schultz): Solid line = sympathetic (dilator); fine dotted line = oculomotor (constrictor); coarse dotted line = trigeminal.

1. The iris contains two sets of smooth muscle-fibers, the sphincters and dilators.

2. The former (sphincters) are innervated by fibers contained in the *oculomotor.* These terminate around the cells of the *ciliary ganglia.* From here the fibers pass as the *short ciliary nerve.*

3. The nerve-fibers for the dilators run in the *cervical sympathetic* and terminate in the *superior cervical ganglion.* The fibers which arise from here go direct to the dilator muscle without passing through any other cells. They run to the Gasserian ganglion, where they join the first branch of the trigeminal, and go from here as the *long ciliary* to the muscle.

The superior cervical ganglion also gives off fibers which go to the internal carotid, and, therefore, influence the blood supply of the eyeball.

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[1] Exercise 54.

The pupils may, therefore, be affected through the following mechanisms:

(A) DILATOR MECHANISM.	(B) CONSTRICTOR MECHANISM.
1. Sympathetic center.	7. Oculomotor center.
2. Sympathetic and long ciliary nerve.	8. Oculomotor and short ciliary nerves.
3. Superior cervical ganglion.	9. Ciliary ganglion.
4. Post-ganglionic fibers.	10. Post-ganglionic fibers.
5. Endings in radial muscle.	11. Endings in sphincter muscle.
6. Fibers of radial muscle.	12. Fibers of sphincter muscle.

Stimulation of "A" causes dilatation; paralysis, constriction through the unopposed action of constrictor mechanism.

Stimulation of "B" causes constriction; paralysis, dilatation through the unopposed action of the dilator mechanism.

(*b*) In the case of *atropin* it may be shown:

1. That the *action is local,* for:

(*a*) It remains confined to the eye, and even to that side of the eye to which it is applied.

(*b*) It can be produced on the excised eye of a frog and even on the isolated iris.

2. Of local mechanisms, we can at once *exclude direct paralysis of the muscle-fibers,* for these can be shown to be active by direct electric stimulation.

3. There remains only stimulation of the endings of the sympathetic, or paralysis of those of the motor oculi.

If the oculomotor nerve is stimulated after atropin, the pupil does not contract, as it would in normal animals. Stimulation of the ciliaris brevis (*i. e.,* peripheral to the ganglion cells) is also ineffective. *The atropin mydriasis is therefore produced by paralysis of the oculomotor endings.*

This does not exclude a simultaneous stimulation of the *sympathetic;* but there are absolutely no facts in support of the latter theory. It is true that section of the sympathetic causes some constriction, even after atropin. This is due merely to the cutting off of the *normal* dilator impulses. It has also been argued that the atropin dilation cannot be a passive process, for it is of sufficient force to tear firm adhesions of the iris. Whilst this is perfectly true, it does not prove stimulation of the sympathetic by atropin, for it is believed that the normal sympathetic impulses are sufficient to produce this result, when they are not opposed by the oculomotor tone. The fact that atropin does not stimulate any other peripheral nerve also speaks very strongly against sympathetic stimulation; so also does the further dilation of the atropinized pupil by electrical stimulation of the sympathetic.

In birds, the iris is not affected by atropin, since it consists of striped muscle.

The statement that the muscular fibers are not affected by atropin must be limited to moderate doses. In greater concentration (according to most observers) it at first stimulates them, producing a temporary narrowing of the pupil; later it paralyzes them.

Direct application of very strong solutions to the ciliary ganglion also depresses this structure.

The *loss in power of accommodation* is also the effect of the oculomotor paralysis. *Increase of intraocular tension* usually accompanies oculomotor paralysis. The mechanism of this is still disputed. The most likely theory is that the muscular contractions occlude the efferent lymph-channels.

All these actions on the eye are produced on systemic as well as on local application. The mechanism is the same in both cases. On local application, atropin takes about one-half hour to fully dilate the pupil, and still longer to paralyze the accommodation; its action persists for some time, often several days. Even dilutions of 1 : 100,000 have some action, but the maximum is only reached with 1 : 100.

With homatropin the effects appear and disappear much more quickly; it is therefore better adapted for purposes of diagnosis, whereas atropin finds its proper use when it is wished to keep the pupil dilated for some time (iritis).

(C) The innervation of **smooth muscle** in other situations is paralyzed in the same manner as that of the sphincter of the iris.[1]

1. **Intestine.**— Very small doses of atropin often (but not always) increase peristalsis somewhat. Jacoby has shown this action to be peripheral, probably a direct stimulation of the muscle fibers. *Ordinary doses arrest normal peristalsis,*[2] as also the increased peristalsis caused by nerve-stimulation, such as the peristaltic reflexes, muscarin, pilocarpin, nicotin, or electric vagus stimulation.

Some investigators, however, claim that atropin does not lessen the peristaltic effects of electric vagus or splanchnic stimulation.

Since moderate doses of atropin do not act directly on the muscle-fibers, direct stimulation of these (electric, physostigmin or some irritant cathartics) is still effective. Large doses also paralyze the muscle, after previous stimulation.

A precisely similar action occurs on that part of the *esophagus* which is composed of unstriped muscle.

2. On the smooth muscle of the *stomach, spleen, bladder, and uterus,* it acts only when they are tetanically contracted (as by muscarin or pilocarpin). Physostigmin is, of course, still active.

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[1] Consult, however, Exercise 66.

[2] Exercise 67.

3. An exception to this nervous paralysis of unstriped muscle seems to exist in the case of *blood-vessels,* at least with moderate doses. In large doses it paralyzes these also, as can be shown by a larger outflow from isolated organs.

(D) Action on the **heart:**[1] Atropin produces a paralysis of the vagus endings at or beyond the point where they are stimulated by muscarin. Stimulation of the vagus trunk or of the sinus therefor causes no slowing; it may, in the frog, produce an acceleration, since the accelerator fibers are not paralyzed by this drug. In animals in which the vagus is normally active (dog, and especially man) its paralysis will result in a greatly quickened heartbeat (in man there is a difference with age, the vagus being most active in middle life, less in old age, and least in infancy). In animals in which the vagus is not constantly acting (frog and rabbit) atropin will not change the rate. (Sodium iodid has a similar action on the vagus endings.)

It must not be forgotten that the cardiac centers in the medulla are also stimulated by the atropin. This is practically overshadowed by the peripheral action. But it may result in a primary slowing.

The action of the other members of the group upon the heart is very similar, belladonnin being the weakest.

Atropin also has a slight direct effect on the *cardiac muscle,* which can be observed in the isolated heart (Fig. 55 *B*), and also on the nerve-free heart of the embryonal chick. Small doses stimulate the muscle, causing an increased tonus, greater excursions, and some slowing. An exhausted frog's heart may be made to beat again. Large doses diminish the tonus and may slow or quicken the rate. Finally the heart is paralyzed, but only after the vasomotor center. Indeed, the effects on the heart muscle are not of any importance in the systemic action of the drug, being overshadowed by the other effects.

Stimulation of a dog's vagus after atropin produces a moderate fall of blood-pressure, due to inhibition of vasomotor tone from excitation of the *depressor fibers* which are carried in the vagus.

(E) **Vasomotor Action.**— The quickening of the pulse is the principal effect of *moderate doses* of atropin on the circulation (Fig. 55 A). The *blood-pressure* is scarcely altered, but there may be a slight rise, from stimulation of the vasomotor center. (The pressure is not altered by atropin if the spinal cord has been divided.) This stimulation is always slight, and may be entirely absent; it is replaced by vasomotor depression rather early.

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[1] Exercise 50.

Large doses depress the vasomotor center profoundly, so that the pressure falls very low, whilst the heart is still beating. Still larger doses paralyze the heart-muscle as well.

Another effect on the circulation consists in an intense *scarlet flushing of the skin,* particularly of the face and thorax, occurring as extensive erythematous spots, or as a continuous scarlatinal erythema. This effect is much greater in some patients than in others; it may occur with therapeutic doses. It is due to dilatation of the cutaneous vessels (vasodilator stimulation), with increased general blood pressure. This hyperemia may be so intense as to lead to desquamation.

(E) Of other peripheral actions, a *curare effect* on skeletal muscle endings in frogs (but not in mammals) may be noted.

Applied directly to *skeletal muscle* it causes a stimulation, expressed by greater excitability and increased height of contraction. Larger doses have the opposite effect. A similar effect has been noted with *cardiac muscle* (see page 234) and with *smooth muscle;* in the latter moderate doses quicken the contraction and slow the relaxation.

The injection of large doses of atropin into the portal vein lowers the *coagulability of blood,* first that of the hepatic vein. This effect cannot be produced by injection into the jugular vein, nor by addition of atropin to shed blood (Doyon and Kareff, 1904), and is due to an action on the liver. The *leucocytes* are not changed.

The *sensory nerves* are dulled on local application, after the manner of cocain.

IV. TOXICOLOGY.

(A) Symptoms.— Atropin being absorbed very readily (and even from the intact skin), the *symptoms appear quickly*. The first to be noticed are those arising from *dryness of the mouth* and throat: difficulty of deglutition and articulation, great thirst, a sense of burning and constriction in the throat. On the eyes, the dilatation of the *pupils,* impaired vision, and absence of reaction to light will be noticed. There is often *nausea* and sometimes vomiting. *Excitement,* passing into delirium, is a prominent feature. The delirium is usually pleasing, with spectral illusions, but may become furious. The onset of the *paralytic symptoms* is ushered in by giddiness, numbness of the limbs, and staggering gait, and passes into drowsiness and stupor. The *pulse* is quick and small. Scarlet flushing of the face. In *fatal cases* death is preceded by coldness of the extremities, rapid and intermittent pulse, and deep coma. Convulsions are rare. Glycosuria is sometimes seen and may be attributed to the asphyxia.

The *postmortem* findings are those of asphyxia.

A fatal ending is, however, quite rare (12%). Violent symptoms may last for days, and it has happened that patients have been consigned to the insane asylum on a mistaken diagnosis. The smallest recorded lethal dose is 120 mg. of atropin.

A psychic "slowness," disturbance of vision, and some other symptoms, may persist for weeks. On account of the slow course and the obscure symptoms, belladonna was a favorite with professional poisoners in the middle ages, and this abuse in regard to several species of Datura has existed in India since remote ages. The name itself is Sanskrit (Dhatoora).

The *local use of atropin in the eye* may give rise to general symptoms, especially if the lachrymal ducts are very patent. Continued administration may lead to conjunctivitis.

(B) The **prognosis,** when properly diagnosed, is favorable, since there is ample time for interference. The **treatment** resolves itself into chemic neutralization, prompt removal, and meeting the symptoms. The delirium is best treated by the ice-cap, the general symptoms by pilocarpin (one-sixth grain hypodermically until mouth is moist). Morphin is also indicated in the early stages, but not after depression has set in. The latter is combated by the usual medullary stimulants (see p. 180). Artificial respiration should be kept up persistently, if necessary.

The effects on the eye may be abolished by the local application of physostigmin.

The **excretion** of the atropin occurs through the urine, for the most part in less than thirty-six hours; and the application of a drop of this fluid to the eye of a cat forms the most handy test for poisoning. The excretion is, however, far from complete; about ⅔ being destroyed in the dog. None is excreted as tropin. Hyoscin is also excreted by the urine.

Atropin resists *putrefaction* for a long time, and may be found in the cadaver even months after burial. Confusion with ptomatropin must be guarded against.

Continued use of small doses seems to establish partial **immunity** to its action. It loses its effect first upon the salivary glands, then on the heart and intestine, and lastly on the eye.

Children bear proportionally larger doses than adults; and the same is true of young animals. Certain classes of animals present a marked *racial immunity* to the atropin group.

Rodents* and marsupiads are very tolerant, as also, to a less extent, the goat, dog, birds, and some other animals. The immunity is in no case complete. It is perhaps greatest in the case of rabbits. Several generations of these animals have been raised on a diet consisting exclusively of belladonna and stramonium leaves. The meat of such animals has produced toxic symptoms in man, so that the *cause of the tolerance* does not consist in increased excretion. Nor do such animals contain any antitoxin, for their serum does not protect less immune animals. The intracerebral injection of leucocytes of immune atropinized animals has been stated to be toxic to other rabbits, and it was concluded from this that the atropin is fixed in the leucocytes. But it has been shown that the leucocytes of an unpoisoned animal produce identical effects; nor could any storage of atropin in leucocytes be demonstrated chemically. The racial tolerance of atropin is therefore unexplained, and must be classed as a histogenetic tolerance.

V. OTHER MEMBERS OF THE ATROPIN GROUP.

There are strong reasons for the belief that ordinary atropin is a racemic compound of l. and d. hyoscyamin. Cushny (1903) has shown that its action corresponds to the sum of its two constituents. These two hyoscyamins agree quantitatively in their effect on the central nervous system of mammals, on the heart muscle, and on motor endings. The levo (ordinary) hyoscyamin alone acts on the endings of the salivary gland, heart, and pupils; whilst it has a weaker stimulant action on the spinal cord of frogs. The two hyoscins show similar differences: they act alike on the central nervous system and motor endings, but the left (scopolamin) is twice as active on the salivary and vagus endings, as the racemic atroscin (Cushny and Peebles, 1905).

Hyoscyamin therefore surpasses atropin in the salivary, vagus, and pupillary actions. The two alkaloids are about equal in their central effect and in their action on the cardiac muscle.

Hyoscin (Scopolamin and Atroscin) are related to atropin in their action, but show important practical difference: The psychic effects show but little stimulation, and considerable depression, so that they are *efficient hypnotics,* resembling morphin. They produce mydriasis, stimulate respiration, paralyze the vagal and gland endings, and stimulate the heart muscle, like atropin.

The action of *homatropin* on the eye was discussed previously.

Relation to Other Groups.—*Cocain:* Constitution, effect on central nervous system and peripheral nerves.

Caffein and strychnin: Stimulating effect on central nervous system. The connection with *nicotin,* etc., groups will be discussed later.

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* Exercise 28.

VI. THERAPEUTIC USES.

(A) The effects of atropin on the **central nervous system** are sometimes used in *psychic depression,* especially in morphin-poisoning (p. 109), as also in mental disease. Since it does not act nearly as promptly or strongly as strychnin upon the medullary centers, it is of but little use in shock.

Hyoscin (*Scopolamin*) is a useful *sedative and hypnotic,* especially in maniacal excitement and delirium tremens. In these conditions hyoscin must be preferred to morphin, since it lessens the motor disturbance, which is only increased by morphin, and it has the advantage over chloral of a slighter depression of the medullary centers. It has little taste, so that it can be easily administered. It is much better borne by insane patients, to whom doses of 1 to 3 mg. ($^1/_{60}$ to $^1/_{20}$ grain)! have been given. With ordinary individuals, 0.5 mg ($^1/_{120}$ grain) should not be exceeded. Very small doses (0.2 mg., $^1/_{300}$ grain) are sometimes employed to enhance the hypnotic effect of morphin. Doses of 0.25 mg. ($^1/_{240}$ grain) have been found useful in the *tremors* of paralysis agitans, lead poisoning, etc., and in spasmodic affection, such as torticollis.

Small doses of atropin (1 mg. = 160 gr.) or of hyoscin (0.5 mg. = $^1/_{120}$ grain) are useful as a *preliminary to general anesthesia.* They are usually combined with morphin (0.01 Gm. = $\frac{1}{6}$ gr.). They stimulate the respiratory center, check the excessive formation of mucus, and prevent reflex stoppage of the heart from vagus stimulation. Atropin is therefore especially useful with chloroform anesthesia, and in operations about the neck. Hyoscin also aids the anesthesia directly.

Schneiderlin and *Korff* have also advocated the hypodermic injection of a mixture of scopolamin (0.3 mg.) and morphin (8 mg.) as sufficient to produce general anesthesia, without ether. Three of the above doses are administered; the first 2½ hours, the second 1½ hours, and the third ½ hour before operating. Complete insensibility results and lasts for ¾ to 14 hours. Post-operative vomiting is common. Some patients, however, do not become anesthetized, and others exhibit severe morphin poisoning. The method can therefore not be advised, especially as the degree of anesthesia cannot be modified to suit the needs of the moment.

(B) Of the **peripheral actions,** those upon the eye are the only ones which can be obtained quite pure; but by carefully adjusting the dose, some of the other actions may also be utilized. The following *dosimetric table* (Schmiedeberg) will be found useful in this connection:

Mg.	Gr.	Symptoms.
0.5 to 1	1/120 to 1/60	Dryness in mouth, often with thirst.
2	1/30	Pupil dilated, not quite immobile. Increase of pulse-rate.
3 to 5	1/20 to 1/12	Headache. Dysphagia. Alteration of voice. Muscular weakness. Restlessness.
7	1/10	Considerable dilatation of pupils. Disturbance of vision.
8	1/8	Excitement and muscular incoordination more marked.
10	1/6	Apathy. Hallucinations or delirium. Unconsciousness.

Except for use on the eye, it matters little which tropein is employed to secure a peripheral action; in practice, atropin is usually given the preference.

(a) **Eye:** mainly for dilating the pupil.

1. For *ophthalmologic examinations* the preference should be given to homatropin, since its effects set in and disappear more quickly. It is used in 1% to 2% solution, dropped on the cornea.

2. In *iritis,* to secure rest, to prevent adhesions of the iris to the lens, or break them if already formed, and to effect assumed favorable changes in the circulation of the iris. The more prolonged action of atropin causes it to be preferred for this purpose.

Atropin is used in solution of 1 : 1000 to 1 : 100. Complete paralysis of accommodation is obtained in about an hour, and partially persists for several days. The dilatation of the pupils occurs much more promptly.

It must not be forgotten that these substances are harmful in glaucoma, as they increase the intraocular tension. They may also give rise to slight general symptoms (headache, dryness of mouth, palpitation).

(b) **Suppression of secretions.**— Atropin is used to check excessive secretion of saliva, sweat, bronchial or nasal mucus, and milk. It gives prompt results, but they are merely symptomatic. The cause of the trouble should be sought and removed. Its (*antisalagogue*) action on the saliva is employed in stomatitis and in various intoxications (mercury, pilocarpin, etc.). Its effect on the nasal mucosa is utilized in acute *coryza.* It is quite efficient in *bronchitis,* by lessening the sputum; and in *bronchial pneumonia,* where it helps also by stimulating the respiratory center. For this purpose, it is best given by inhalation of an atomized solution.

Its (*anhydrotic*) effect on sweat is mainly useful in the *night-sweats of phthtisis*. Small doses (0.3 mg. = $^1/_{200}$ grain) are employed. Hyoscin can be substituted.

The following drugs are used in the *treatment of night-sweats:*

1. *Atropin Group:* paralyzing the secretory endings; atropin ⅓ to 1 mg.

2. *Agaricin:* The action is peripheral, and probably resembles atropin, but is much weaker. It appears in a few hours, and is not lasting. Habituation occurs, so that it is best to begin with small doses (0.5 mg.) and increase gradually to 40 mg. per day. Large doses cause diarrhea, vomiting, and death through central paralysis. It does not act on any other glands. *Sodium Tellurate* appears to act similarly, but is objectionable on account of the persistent garlic odor which it gives to the breath.

3. *Picrotoxin,* 1 to 3 mg.

4. *Camphoric Acid,* 1.5 to 2 Gm. in wafers.

Picrotoxin and camphoric acid act by stimulating the respiratory center, and are especially useful if the sweat is asphyxial; *Menthol,* 0.1 Gm., belongs to the same class. Cold *brandy* is sometimes used, but is of doubtful value.

The drugs are taken in the evening, before retiring. Atropin is by far the most efficient, but its side-actions interfere greatly with its use. *Local measures* are often useful: Sponging with cold lotions containing alcohol, dilute acids, or astringents (salicylic acid); the last may also be used as dusting powder, mixed with 20 parts of talcum. Tannoform (with 2 parts of talcum) has been recommended.

(c) **Peristalsis.**— Atropin may be used to stop a *diarrhea* which depends upon central influence, but is useless if the cause lies in the intestine itself. It will, on the other hand, be useful in constipation from tonic spasm of the intestine (*e. g., lead colic*), just like morphin; 0.75 mg. ($^1/_{80}$ grain) often gives prompt relief in the colic pains of indigestion. It is frequently added to irritant *laxatives,* since, by preventing local contractions depending upon nervous stimulation, it obviates griping, and it does not, at the same time, interfere with the purgative action of the irritants (see Chapter XXX.). Small doses may be directly laxative by stimulating the intestinal muscle. Preparations of the *crude drug* should be used for local action on the intestine.

The paralysis of unstriped muscle is also taken advantage of for the relief of *biliary and renal colic* from calculi. The vagus paralysis is also useful in this connection in preventing the dangerous slowing of the heart which sometimes occurs. *Incontinence of urine,* when due to overaction of the bladder muscle, is also relieved by it, as may also be retention of urine due to overaction of the sphincter. Its action on the *uterus* is so uncertain that its value in treating tetanic contraction of this organ is doubtful.

(d) The **paralysis of the cardiac vagus endings** indicates it in all conditions in which slowing or even stoppage of the heart from stimulation of the inhibitory mechanism exists. This may occur in *pressure of the brain,* and in other conditions which we have already discussed.

(e) Another use of atropin is as a **local application,** usually in the form of liniment or plasters, for the *relief of pain.* The modus operandi has been discussed, but it is inferior in this respect to cocain, on the one hand, and counterirritants on the other (see Chapter XXIX). The antagonism of atropin and iodothyrin (see Chapter XIII) indicates it in Basedow's disease or thyroid poisoning.

One of the most important uses of atropin is found in the treatment of **asthma.**

Asthma consists essentially in a *spasmodic constriction of the bronchioles,* which may be produced reflexly (*e. g.,* by irritation of the mucosa of the nose, larynx or bronchioles); or directly by electric stimulation of the vagus trunk;[1] by drugs stimulating the endings of the vagus in the bronchial muscle (muscarin, pilocarpin, physostigmin, neurin, digitalin, aspidospermin); by drugs acting on the bronchial muscle (barium, veratrin, salts of many metals, bromin vapor); or by central actions (CO_2). In the disease, asthma, there is perhaps also a catarrhal congestion of the mucous membrane, but the bronchial spasm is the predominating feature.

This is promptly relieved by *drugs which dilate the bronchi,* viz.: atropin, hyoscyamin, hyoscin, chloroform, ether, urethane, cyanids. Small doses of morphin also cause dilation, but large doses constriction. The following drugs dilate after producing a temporary constriction: lobelia, nicotin, curare. Suprarenal and ergot have little action (Dixon & Brodie, 1903).

The pharmacologic data throw considerable light upon the *therapeutic treatment of asthma,* for which the following drugs have been used:

Atropin: relieves the bronchial spasm by paralyzing the motor endings of the vagus. It also lessens secretion, lowers the sensitiveness of the mucous membrane to reflexes, and stimulates the respiratory center. The dose is ½ to 1 mg. It is often used by inhaling the smoke of burning stramonium leaves, mixed with potassium nitrate. The empyreumatic products of smoke probably have a dilator action also, so that the burning of paper impregnated with nitre (*Charta Potassii Nitrates*) is of some benefit. It is conceivable that *nitrites* have a similar action, but they may also be beneficial by altering the distribution of blood. Hyoscyamus, belladonna, lobelia, tobacco, and spartein are sometimes mixed with stramonium, or are substituted for it; they act in a similar manner. Sometimes one of these drugs gives better results than the others.

Chloroform, ether, and *morphin* act similarly, but are not as effective. They are also useful by lessening the discomfort and apprehension of the patient.

The effective lumen of the bronchioles can also be widened by expelling whatever mucus is contained in them. *Emetics and nauseants,* particularly *potassium iodid* (1 to 3 Gm. per day) act in this manner. (*Ergot* is said to be useful in some cases, but its use has no rational foundation.)

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[1] The vagi also carry dilator fibres, but the constrictors predominate. Stimulation of the sympathetic has no effect on the bronchial muscles.

The *cause of the disease* lies often in an irritation of mucous membranes, which can be relieved.

When gross changes, especially of the nose or pharynx, can be demonstrated, these should be removed. When the condition is one of increased susceptibility to unavoidable irritants (as to pollen in hay-fever), this may be lowered by cocain, or mechanical protection afforded by ointment. An antitoxic serum has also been introduced (see Index, pollantin).

The asthma may also be treated through the *respiratory center*, by two diametrically opposed sets of remedies:

1. By depressants, through (*a*) lowering the reflex excitability of the centers concerned in the production of the attack.

(*b*) By narcotics, through diminishing the discomfort of the patient.

Both indications are met by morphin, codein, alcohol, chloroform, KBr, HCN.

2. By stimulants, through increasing the activity of the respiratory center when it has become exhausted through the violence of the attack.

Among stimulants, caffein, strychnin, and atropin stand foremost for this purpose. The same result may be achieved through counter-irritation (ammonia, sinapism).

Finally much of the discomfort of the patient may be removed symptomatically, by the inhalation of oxygen or compressed air (Chapter XX, B).

VIII. MATERIA MEDICA.

(A) — U. S. P. PREPARATIONS.

All the plants belong to the family Solanaceæ. With the exception of stramonium leaves, and the liniment and plaster of belladonna, the crude drugs and their preparations deserve to be abandoned, and atropin or scopolamin substituted.

Crude Drugs (the minimum percentage of total alkaloids is given in brackets):

Belladonnæ Folia and *Radix.*— From *Atropa Belladonna.* Deadly nightshade; Europe and Asia Minor. [Leaves, 0.35%; Root, 0.5%.]

Hyoscyamus.— Leaves of *H. niger,* Henbane; Europe and Asia. [0.08%.]

Scopola.— Rhizome of *S. Carniolica.* [0.5%.]

Stramonium.— Leaves of *Datura Stramonium,* Thornapple, Jamestown Weed; originally from Asia, naturalized in many countries. [0.35%.]

Stramonium leaves, mixed with 10% of saltpeter, are used for asthma, the mixture being ignited and the smoke inhaled.

NOTE.— Belladonna, Scopola, and Stramonium contain approximately the same percentage of alkaloids (0.35 to 0.5%), but Hyoscyamus is weaker. It also differs from the preceding by the relative predominance of hyoscin.

Preparations:

The *strength* of the preparations is adjusted to the minimal content of alkaloids (*e. g.*, Belladonna Leaves, 0.35%); the tinctures containing $^1/_{10}$, the extracts four times this quantity). The preparations are miscible with water and alcohol. The *extracts* are generally prepared by the evaporation of the fluidextracts. They have a pilular consistency.

Dose: The corresponding preparations of Belladonna, Scopola, and Stramonium have the same dose. Those of Hyoscyamus preparations are somewhat larger.

	List of Official Preparations.	Dose.	U. S. P.
Belladonna Leaves:	*Tinctura Belladonnæ Foliorum*	0.3 to 1 c.c. (5 to 15 ♏.)	0.5 c.c.=8 ♏.
	Extractum Belladonnæ Foliorum	5 to 15 mg. (1/10 to ¼ gr.)	10 mg.=⅕ gr.
	Unguentum Belladonnæ	10% of extract (leaves)	
	Emplastrum Belladonnæ	30% " " " in adhesive plaster.	(0.38 to 0.42% of alkaloids)
Belladonna Root:	*Fluidextractum Belladonnæ Radicis*	0.05 to 0.2 c.c. (1 to 3 ♏.)	0.05 c.c.=1 ♏.
	Linimentum Belladonnæ Radicis	5% of camphor, dissolved in the fluidextract.	
Hyoscyamus:	*Tinctura Hyoscyami*	0.5 to 1.5 c.c. (8 to 25 ♏.)	1 c.c.=15 ♏.
	Fluidextractum Hyoscyami	0.15 to 0.3 c. c. (2½ to 5 ♏.)	0.2 c.c.= 3 ♏.
	Extractum Hyoscyami	0.05 to 0.1 Gm. (⅔ to 1½ gr.)	65 mg.=1 gr.
Scopola:	*Fluidextractum Scopolæ*	0.05 to 0.2 c.c. (1 to 3 ♏.)	0.05 c.c.=1 ♏.
	Extractum Scopolæ	5 to 15 mg. (1/10 to ¼ gr.)	10 mg.=⅕ gr.
Stramonium:	*Tinctura Stramonii*	0.3 to 1 c.c. (5 to 15 ♏.)	0.5 c.c.=8 ♏.
	Fluidextractum Stramonii	0.05 to 0.2 c.c. (1 to 3 ♏.)	0.05 c.c.=1 ♏.
	Extractum Stramonii	5 to 15 mg. (1/10 to ¼ gr.)	10 mg.=⅕ gr.
	Unguentum Stramonii	10% of extract.	

Alkaloids.—The *average dose* of the alkaloids is 0.5 mg.=1/128 gr. The salts are freely soluble. They are used in 1% solution for dilating the pupil. The solutions deteriorate on keeping.

Study Materia Medica Lesson 22.

Atropina, $C_{17}H_{23}NO_3$.— Contains some hyoscyamin. Sol. 450 water, 1.46 alcohol. *Dose:* 0.4 to 2 mg. ($^1/_{100}$ to $^1/_{30}$ gr.) (0.4 mg. = $^1/_{100}$ gr., U. S. P.).

Atropinæ Sulphas, $Atr._2.H_2SO_4$.— Sol. 0.38 water, 3.7 alc. *Dose:* as the preceding.

Oleatum Atropinæ.— 2%.

Hyoscyaminæ Hydrobromidum, $C_{17}H_{23}NO_3.HBr$.— Very soluble in water, and in 2 parts alcohol. *Dose:* as Atropin (0.5 mg. = $^1/_{128}$ gr., U. S. P.).

Hyoscyaminæ Sulphas, $Hy_2.H_2SO_4$.— Very soluble in water and in 6.4 parts alcohol. *Dose:* as the preceding.

Homatropinæ Hydromidum, $C_{16}H_{21}NO_3.HBr$.— Sol. 5.7 water, 32.5 alc. *Dose:* as the preceding.

Hyoscinæ / *Scopolaminæ* } *Hydrobromidum* (identical), $C_{17}H_{21}NO_4.HBr + 3H_2O$.— Sol. in 1.5 water, 16 alc. *Dose:* 0.3 to 0.6 mg. ($^1/_{200}$ to $^1/_{100}$ gr.) (0.5 mg. = $^1/_{128}$ gr., U. S. P.).

(B) — B. P. PREPARATIONS.

Consult the U. S. P. lists for details.

Crude Drugs.— Belladonnæ Foliæ and Radix; Hyoscyami Folia; Stramonii Folia and Semina.

Preparations:

Belladonnæ Leaves (fresh).— EXTRACTUM BELLADONNÆ VIRIDE (¼ to 1 gr.); SUCCUS BELLADONNÆ, 5 to 15 ♏.

Belladonna Root.— EXTR. BELL. ALCOHOL.: (1% of alkaloids) ¼ to 1 gr.; EXT. BELL. LIQ. (¾% alk.); TINCT. BELLAD. ($^1/_{20}$% alk.); LINIM. BELLAD.; UNG. BELLAD.; EMPL. BELLAD.; SUPPOS. BELLAD. ($^1/_{100}$ gr. alk.).

Hyoscyamus (fresh leaves).— EXT. HYOSC. VIR. (2 to 8 grs.); TINCT. HYOSC. (½ to 1ʒ); SUCCUS HYOSC. (½ to 1ʒ).

Stramonii Folia.— TINCT. STRAM. (5 to 15 m.)

Stramonii Semina.— EXT. STRAM. (¼ to 1 gr.).

Alkaloids.— *Atropina;* Atropinæ Sulph.; Ung. Atropinæ (4%); Liq. Atropinæ (1%); Lamellæ Atrop. ($^1/_{5000}$ gr.).

Hyoscyaminæ Sulphas.

Hyoscinæ Hydrobromidum.

Homatropinæ Hydrobromidum; Lamellæ Homatropinæ ($^1/_{100}$ gr.).

Synthetic Mydriatics.— * *Eumydrin* (Atropin methyl nitrate) has been investigated by Dreser and by Goldberg It is said to have only $^1/_{50}$ the danger of atropin; its general actions agree with the latter; but it is claimed that it does not raise the intraocular pressure (?) whilst the promptness and duration of the mydriasis lies between atropin and homatropin.

* *Euphthalmin* (Hydrochlorid), the mandelic ester of beta-eucain, has mydriatic properties, and is recommended as a substitute for homatropin, in strength of 2 to 10%. It causes no irritation, and only moderate loss of accommodation, and does not raise the intraocular tension. The effect is quick and short. It forms a white, crystalline powder, readily soluble in water.

CHAPTER XII.

MUSCARIN-NICOTIN-CURARE SERIES.

(A) MUSCARIN GROUP.

I. STRUCTURE, DERIVATION, AND OCCURRENCE.

The muscarin groups contain a number of alkaloid and ptomain principles, which are chemically derived from cholin. This is formed by the combination of glycol and trimethylammonium, with the elimination of H_2O:

$$\underset{\text{Glycol.}}{C_2H_4OH}\ \boxed{OH + H}\ \underset{\text{Trimethyl Ammoniam}}{N(CH_3)_3OH} = H_2O + \underset{\text{Cholin.}}{C_2H_4OH - N(CH_3)_3OH}$$

In the other members of the group (isocholin, muscarin, neurin, betain), the $N(CH_3)_3OH$ remains intact, the changes occurring in the C_2H_4OH — *f. i.,* in muscarin by the addition of O. (first edition, p. 267).

These substances are mostly formed in the putrefaction of nitrogenous matter, by the action of bacteria. They are, indeed, among the principal members of the group of "putrefactive alkaloids" or "*ptomains.*" But they are also formed in living plants, and especially in fungi. Muscarin, the typical member of the group, is contained in the fly-agaric, Agaricus (Amanita) muscarius, growing in birch and pine woods in many parts of the globe. It probably occurs also in some of the other poisonous fungi, but this has not been sufficiently investigated; one of the characteristic features of the members of this group — and of ptomains generally — is the ease with which they are decomposed, and this renders their investigation very difficult. One of the decomposition products of muscarin seems to have an atropin action, so that many samples are entirely worthless.

II. SUMMARY OF ACTIONS OF MUSCARIN.

1. Stimulation of precisely those peripheral structures which are paralyzed by atropin. This stimulation is peculiar in not being followed by depression.
2. Affections of the central nervous system, as yet imperfectly studied.
3. A curare effect on motor endings, very inconspicuous in the case of muscarin itself.

There is no effect upon ganglia or nerve-fibers, even when the drugs are directly applied.

III. DETAILS OF ACTION.

1. **Heart.**— Muscarin causes *slowing* and stoppage in diastole, just as in electric vagus stimulation. The effect is more persistent than with the latter. This standstill occurs also in the isolated apex, showing that the stimulation is peripheral to the ganglia; and since it can be abolished by atropin or sodium iodid, the action cannot be on the muscle. It is therefore assumed that it stimulates those endings which atropin paralyzes. If muscarin and atropin are exhibited at the same time or successively, their respective quantity will determine which predominates. Drugs which act upon the ganglia — *e. g.*, nicotin — will be ineffectual; but the standstill may be raised by substances effecting a direct stimulation of the muscle-fibers — *e. g.*, physostigmin, veratrin, digitalin, anilin, camphor, guanidin.

The same stimulation of the vagus endings can be obtained by *iodothyrin.*

It is interesting that muscarin causes an acceleration of the crab's heart, although a well-defined inhibitory mechanism exists in these animals. The explanation undoubtedly lies in some structural peculiarity.

The action of muscarin on *muscle*-substance is precisely opposed to atropin. On skeletal muscles (curarized or not) it resembles veratrin, causing a slow relaxation; the contractility is lowered with large doses, but spontaneous contractions appear. Its action on the heart muscle leads to increased tonus and greater excursions.

2. The effects upon the **eye** (exclusive stimulation of oculomotor endings), **glands, and unstriped muscle** in general are precisely the same as with pilocarpin. As to the *intestine,* small doses cause a stimulation of Auerbach's plexus: strong contraction and paling of the whole intestine. This is inhibited by atropin and by extremely large doses of the muscarin itself. It produces asthmatic dyspnea by contraction of the bronchial muscles.

The muscarin group has only a scientific and *toxicologic importance.* Poisoning by mushrooms and meat is largely due to these substances.

(B) MUSHROOM-POISONING.

This topic still requires much elucidation. Undoubtedly different, although related, active substances are present in the various mushrooms as well as in different samples of spoiled meat. Even the fly agaric contains another convulsant poison, probably a toxin.

The **symptoms** are accordingly quite variable. Features which are more or less common to mushroom-poisoning are: Abdominal pain, nausea, vomiting, and violent diarrhea; variable pulse; labored respiration; consciousness unaffected, or delirium; coma or convulsions. Some cause fatty degeneration of the liver and kidneys. Many mushrooms produce abdominal symptoms simply by being indigestible.

Poisoning by the fly-mushroom, which has been best studied, presents a close resemblance to that by pilocarpin. The pulse is always slowed, and the blood pressure falls, as also through vasomotor paralysis. Muscular weakness and incoordination are among the more prominent symptoms. Death usually occurs after several days, the cause being yet obscure, but probably residing in the central nervous system.

The **treatment,** besides removal and chemic and symptomatic antidotes, as with pilocarpin, would be by atropin. The chance of poisoning may be somewhat diminished by prolonged boiling, as some of these substances are decomposed in this manner. This does not hold for the Amanitæ. Drying does not diminish the toxicity.

The proof of the poison consists in the demonstration of the physiologic action of the alkaline ether extract. It cannot be demonstrated in the urine.

There seems to be an acquired immunity to the peripheral action of muscarin, as there is to nicotin and atropin: In Kamschatka the fly-agaric is used as an intoxicant, producing symptoms similar to those of alcohol, seemingly without exhibiting its peripheral action.

Pellegrini claims that an antitoxic serum can be obtained, but the statement needs confirmation.

Edible Mushrooms.— The food-value of mushrooms is popularly supposed to lie in a large percentage of assimilable nitrogen. This is not borne out by analyses: they contain 0.1% in the fresh condition, or 0.3 to 1.6 when dried; *i. e.,* no more than potatoes, and only one-tenth as much as wheat bread, or one-thirtieth of that in lean meat. As the fiber of mushrooms is also quite indigestible, their main dietary value is as a relish rather than as food.

(C) CHOLIN, NEURIN, ETC.

These have some little importance as products of putrefaction, forming some of the poisonous ptomains. They are also formed during intestinal putrefaction, and may be absorbed in obstinate constipation in sufficient amount to produce symptoms. They are also found in extracts of nervous matter.

Osborne and Vincent (1900) believe that cholin is not the active ingredient of **extracts of nerve-matter,** for its amount is too small. The nature of the active constituent is not known, but it is neither proteid nor carbohydrate. It also differs from cholin by paralyzing the arterial muscle directly. The other actions agree.

Neurin is much more toxic than cholin. It may be formed from the latter by bacteria.

1. **The peripheral effects** agree with muscarin:

The peristalsis is increased (especially important when formed in the intestine, constituting a kind of natural treatment of intestinal putrefaction).

The heart is slowed (stimulation of the vagus and depression of muscle).

The glands are stimulated (except bile).

Curare action. (This is quite strong, especially in cholin.)

2. They show some differences from muscarin in their **central action:**

They have only a feeble effect on the *brain* and *spinal cord;* considerable on the *medulla.*

The respiration is weakened through depression of the center.

The vasomotor center is first strongly stimulated, then depressed.

The blood pressure follows the vasomotor and cardiac changes.

(D) MEAT-POISONING.

The cases of poisoning observed as a result of partaking of more or less tainted articles of food — sausages (botulismus and allantiasis), meat, milk, ice-cream, cheese, corned beef, etc., and with some specimens of mussels and oysters — are due to the development of ptomain products. In the former cases these are developed by putrefaction; in the latter, probably by disease.

These ptomains have, for the most part, been isolated in crystalline form, and are well defined compounds belonging to the amin series. Their pharmacologic action lies between that of atropin and muscarin.

The **symptoms** may be summarized as follows:

(a) *Gastro-intestinal disturbance:* nausea and vomiting, and either diarrhea or constipation. This is due to the local irritation, and, in addition, to stimulation or paralysis of the local nervous mechanism, and probably to some extent is central.

(b) *Dryness of mouth:* difficulty in swallowing, articulation, etc.; due to paralysis of the nervous mechanism of the salivary and mucous glands.

(c) *Pupil:* dilated by almost all; through an atropin action.

(d) *Heart:* quickened by atropin action.

(e) *Muscular weakness:* partly central; partly, and perhaps mainly, peripheral.

(f) *Sensory:* disturbed sensations of various kinds, formication, heat, etc.; probably central.

(g) *Medullary centers:* depression of respiratory and vasomotor centers, sometimes preceded by stimulation. The vessels of the skin are usually dilated, producing sweating, itching, heat, and erythema.

(h) *Brain:* the consciousness is usually not affected, but there may be delirium and later coma. When convulsions are observed, they are probably always asphyxial.

The perfectly fresh flesh of certain tropic and Russian fishes also produces central symptoms (Signatéra).

Tainted meat is also counted among the causes of scurvy.

The **treatment** in all cases would be mainly symptomatic, and no general rules can be given. Emetics and cathartics should be employed whenever necessary.

(E) PILOCARPIN GROUP.

This group comprises the alkaloids of jaborandi leaves (pilocarpus), viz., pilocarpin, isopilocarpin, and pilocarpidin. These differ merely in the strength of their action, pilocarpin being by far the strongest, and pilocarpidin the weakest. A similar alkaloid, nigellin, is found in Nigella sativa. It was formerly believed that pilocarpus contained another alkaloid, jaborin, with atropin actions. This view has been shown to be erroneous.

I. SUMMARY OF ACTIONS.

1. Stimulation, followed in larger doses by depression, of the peripheral structures which are paralyzed by atropin.

The stimulation is very persistent. The action is mainly on the nerve-endings, but also involves the ganglia and cells.

2. A late and weak stimulation, followed by more con-

spicuous paralysis, of certain parts of the central nervous system.

II. ACTIONS IN DETAIL.

Relation to Atropin, Muscarin, etc.— Small doses of pilocarpin are almost exactly antagonistic to atropin; larger doses, however, are synergistic. This can be best shown in the vagus action (Marshall, 1904), and in their effect on developing ova (Sollmann, 1904). The former involves nervous actions, the latter the direct effect on cells. In the case of glands, the stimulant phase is much more persistent, and the antidotal effect is almost directly proportional to the quantity of pilocarpin.

The effects of small doses of pilocarpin on most organs correspond almost exactly to those of muscarin, although the two alkaloids are not related chemically. Relatively much larger doses of pilocarpin are required to antagonize atropin, because its action is partly ganglionic. It differs from muscarin especially in the fact that the latter is stimulant even in large doses, whilst large amounts of pilocarpin become depressant and therefore antagonistic to muscarin.

(A) Glands.[1]— Pilocarpin produces an increase in the secretion of saliva, sweat, tears, mucus, and of the gastric, pancreatic, and possibly of the intestinal juice.

The effect upon the secretion of milk is doubtful.[2] An increase in the proportion of sugar in the blood has been ascribed to the stimulation of the glycogenic nerves in liver. The secretion of urine and bile is not directly affected (MacCallum, 1905); the considerable loss of fluid by other channels generally diminishes the water and chlorids of the urine (Asher, 1905).

The general increase in the secretions is due mainly to water; but the total solids are also increased, although their percentage is lessened. The amount of water lost in this manner, mainly by the perspiration, is very large — as much as a gallon after a single injection.

The *seat of the stimulation* is mainly in the nerve endings or ganglia.

It is not central, since it occurs after section of the nerves; nor does it reside in the cells, since it can be arrested by atropin, which acts upon the nervous structures only. That it may occur through stimulation of the nerve endings is shown by the fact that in the cat's paw the secretion of sweat is increased by pilocarpin (after division of the sciatic), yet the sweat nerves in this situation possess no ganglia. It is claimed that pilocarpin is effectual two weeks after section of the sciatic. Since the nerves would be degenerated by this time, it would seem that the pilocarpin can stimulate the gland cells directly. But the statement needs confirmation. It is furthermore very probable, that a part of the stimulation involves the ganglia, on account of its action on the heart, where, as we shall see, it stimulates these mainly; and, further, the dose of pilocarpin required to produce secretion after atropin is relatively much larger than that of muscarin (which stimulates the endings), showing that part of its action must be higher up than with the latter.

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[1] Exercise 55.

[2] There are at present no really reliable data concerning the action of drugs (except alcohol) upon milk secretion.

Acceleration of the blood current through the glands occurs as a secondary effect of their increased action. A common effect of pilocarpin, a hyperemia of the skin (resulting in an increase of its temperature), may possibly be due to the increased activity of the sweat-glands.

(B) Unstriped muscle generally (except that of blood-vessels, which appears almost exempt from its action) is thrown into contraction by stimulation of its peripheral nervous apparatus. This is most conspicuous in the *intestine,* resulting in increased peristalsis, diarrhea and colic.[1] It occurs independently of the central nervous system, and is abolished by atropin in the same manner as the secretions. After very large doses, the stimulation is followed by paralysis. An identical action upon the stomach results in nausea, retching, and vomiting, but the effects upon this organ are much less than those upon the intestine. Of other unstriped muscle, that of the *bronchi, bladder, spleen, and possibly of the uterus,* is affected in the same manner.

(C) In the **eye** [2] pilocarpin produces miosis and spasm of accommodation through stimulation of the motor-oculi endings and ganglia, the evidence being the same as in the case of glands. The intraocular tension is at first raised, followed by a more persistent fall, due to the miosis. Large doses produce late paralysis of the oculomotor endings, as elsewhere.[3]

(D) Pilocarpin, applied to the frog's heart, produces stimulation of the vagus ganglia with following paralysis. There is at first diastolic standstill, after which the heart returns to its normal rate. Stimulation of the vagus trunk is now ineffective, but stimulation of the sinus produces stoppage. This shows that the endings are not paralyzed, and the paralysis must therefore be limited mainly to the ganglia; although most observers also claim some affection of the endings in addition.

Very large doses again stop the heart, but since atropin does not remove this final standstill, it is evident that it must be due to direct paralysis of the heart-muscle.

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[1] Exercise 67.
[2] Exercise 54.
[3] Old solutions of pilocarpin may cause mydriasis.

In the *excised mammalian heart* (Hedbom-Langendorff) the action is the same, but the stage of vagus stimulation is short: the rate is suddenly slowed; this lasts but a short time; then there is marked quickening with increased tonus (peripheral paralysis of vagus). Large doses paralyze the muscle.

In those mammals in which the *vagus is constantly acting* — *e. g.*, dog and man — pilocarpin gives a marked acceleration of the pulse, with increased blood-pressure (Fig. 57, *B*) and later with arhythmia. The cause for this must be sought in vagus-paralysis; but the rise of blood-pressure is partly due to a stimulation of the vasomotor center. In large doses this action is followed by muscular slowing and weakening of the heart, and consequently fall of pressure. This action, as in the frog, cannot be removed by atropin, and is on the muscle directly. In rabbits, a short primary vagus *stimulation* precedes the phenomena described for dogs, and makes itself felt by slowing of the heart and fall of blood-pressure; this action sometimes occurs in man and dog (Fig. 57, *A*). Small doses merely increase the excitability of the vagi.

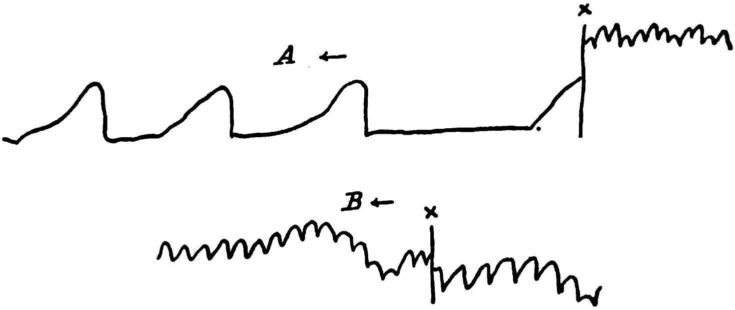

Fig. 57.— Pilocarpin. Carotid pressure, dog. The action begins at ×. *A* shows stimulation of vagus; *B*, depression of vagus.

(E) Central Nervous System.— The action is weak and appears late, so that it is entirely overshadowed by the peripheral actions. The effects are mainly *depressing* (and this applies to the other groups of the series). *Vasomotor paralysis* is a rather early and prominent symptom; it leads to *dyspnea*. Later, the *respiratory center* is also depressed.

Edema of the lungs,[1] consequent on the weakened heart and obstruction of the bronchi by mucus, is a frequent occurrence. The *motor centers,* especially those of the cord, show some stimulation (increased reflexes, tremors, convulsions) and later paralysis.

Metabolism.— Pilocarpin somewhat increases CO_2 production and tends to raise the temperature, even in curarized animals, *i. e.,* by direct stimulation of the glands and unstriped muscle.

III. TOXICOLOGY.

The toxicology of pilocarpin is not very important. The **symptoms,** which apply also to muscarin, begin with a greatly increased secretion of saliva, sweat, and tears; then nausea, profuse vomiting, and painful diarrhea; pupillary contraction and spasm of accommodation; pulse variable in rate, tense, and arhythmic; palpitation; dyspnea with râles; sometimes confusion of ideas, vertigo, tremors, and feeble convulsions. Death occurs either by paralysis of the heart or edema of the lungs.

Untoward effects from the alimentary canal are seen most frequently if the drug is given by mouth, but occur also on hypodermic administration. They consist in very prolonged and depressing nausea and vomiting, sometimes leading to collapse. The disturbance of accommodation causes misty vision. A burning sensation in the urethra, with sudden and irresistible desire to urinate, is often observed.

Treatment.— Atropin is a physiologic antidote. Otherwise the general treatment of alkaloidal poisoning. For materia medica and therapeutic uses, see end of chapter.

(F) CURARE GROUP.[2]

I. MEMBERS, DERIVATION, AND CONSTITUENTS.

The most characteristic action of curare — the paralysis of the nerve-endings in striped muscle — is possessed by many poisons. The curare action is indeed so widely distributed that it may be looked upon as a peculiar expression of fatigue or as a sign of injury to these endings.

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[1] The edema produced by the drugs of this series consists rather in the aspiration of the bronchial effusion, than in a true serous effusion. Injury to the walls of the capillaries is a necessary factor for the latter.

[2] Exercise 42.

Among the most important poisons possessing this action are the following:

Certain ammonia bases, amids and amins, cholin, muscarin, etc.
Methyl-strychnin.
Aromatic series: Pyridin, quinolin, thallin.
Nicotin series, piperidin.
Cocain.
Camphor in frogs, but not in warm-blooded animals.
Certain putrefactive ptomains.
Products of muscle metabolism.

The curare action of many of these drugs can only be demonstrated in frogs, being obscured by other actions in mammals. These are not, therefore, included in the curare group.

Curare is derived from the root-bark of South American plants of the genus Strychnos.[1] It is prepared by the Indians as an arrow poison. The different samples which find their way into commerce probably have quite a different constitution. They are called Tiennas, Woorara, and Curare. Certain of them are also said to contain snake venom, but this appears to be erroneous. All these samples lose a great deal of their activity in time, especially if moist, and commercial curare is a most unreliable drug.

The constituents vary with the origin and also with the length of time during which the drug has been kept. They are alkaloidal in nature. The most important are:

Curarin,
Protocurarin,
Tubocurarin.

They decrease in activitv in the above order, the curarin being the strongest. Curarin is related chemically to strychnin, and these two alkaloids also agree in some of their side-actions.

II. SUMMARY OF ACTIONS.

1. Paralysis of the nerve endings in striped muscles.
2. Later, paralysis of the nerve endings around sympathetic ganglia (vasomotor and vagus).
3. With very large doses a direct depression of the irritability of the muscle substance.[2]
4. Under special conditions a strychnin-like action on the central nervous system.

III. DETAILS OF ACTIONS.

1. Paralysis of Muscle-nerve Endings.— Ordinarily the only symptoms of "curare" poisoning consist in this paralysis. When the curare is introduced under the skin, it causes a total loss of motion, first of the voluntary and then of the respiratory muscles. The order in which this disturbance appears is the following:[3]

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[1] It was first brought to Europe from Guyana by Sir W. Raleigh in 1595.

[2] Some substances with curare-action increase the direct excitability of the muscles but this is not the case with curare itself.

[3] The muscles which are least affected by curare are those which contain the largest amount of utilizable oxygen, and survive longest after the death of the animal. This supply of oxygen accounts, probably, for the lesser susceptibility to the depressing action of curare.

(*a*) Short muscles of the toes, ears, and eyes.
(*b*) Limbs, head, and neck.
(*c*) Respiration.

The heart is not affected except with very much larger doses.

The first sign of curare action consists in incapacity for sustained effort on repeated stimulation of the nerve; *i. e.*, whereas a single contraction is normal, fatigue sets in more readily than usual. Then the height of contraction is somewhat lowered. Then the current must be strengthened to obtain any response; and finally even the strongest stimulation — of the nerve — is ineffectual.

It is evident that some structure is paralyzed. The paralysis might have its seat in any part of the central nervous system or it might be peripheral. Stimulation of the sciatic does not produce a contraction if the dose has been sufficient. The point of attack must, therefore, be peripheral to the sciatic nerve. This leaves the nerve-trunk itself, the nerve endings, and the muscle-fibers. Stimulation of the muscle directly is effective, so that this is excluded. To decide between the nerve-trunk and nerve endings, Bernard in his classical experiment placed a ligature around the body of a frog, with the exception of the sciatic nerves, and tightened the ligature so as to entirely exclude the lower extremities from the circulation. He then injected the curare. In this manner the peripheral portions of the sciatic nerves and the endings did not come into contact with the curare and the nerve-trunk was alone exposed to the poison. He found that stimulation of the trunk caused normal contraction, consequently that curare had no action on it, thus leaving only the endings (Exercise 42).

The experiment can be performed in a much simpler manner by ligaturing one leg exclusive of the nerve, or by placing the muscle of one and the nerve of another muscle-nerve preparation into the solution.

This paralysis does not affect the *sensory nerves.* The reports of early travelers who describe poisoning by curare-arrows mention that sensation is not impaired when motion is entirely impossible. Bernard also studied this action directly on the frog. He ligatured one leg with the exception of the sciatic nerve, injected the poison, and applied the stimulus to one of the upper extremities. This caused a reflex movement of the ligatured leg, which would not have been the case had the sensory endings of the foreleg been paralyzed.

In cold-blooded animals in which the respiratory exchange takes place largely through the skin, and respiratory movements are unnecessary, the poison is gradually eliminated if the animal be kept in a moist atmosphere. Complete recovery occurs after eight to ten days, except when the dose is extremely large, in which case other factors come into play.

Warm-blooded animals die of paralysis of the respiratory muscles. If artificial respiration be kept up and the dose has been only just large enough to produce a paralysis, they may also recover.

The recovery of the respiratory muscle begins immediately, whilst the sciatic endings require several hours. The effect of the curare increases progressively with the dose: it is as if an increasing resistance were gradually introduced between the nerve and the muscle.

The seat of the *respiratory paralysis* is also peripheral, for stimulation of the phrenic nerve does not cause contraction of the diaphragm.

The respiratory paralysis, if it is not too profound, is promptly removed by *physostigmin;* stimulation of the sciatic also becomes effective again. It cannot be decided whether this restorative action of the physostigmin is on the endings or on the muscle (Rothberger, 1901).

Curare paralyzes the *temperature-nerves* of the muscles, as well as the motor nerves, so that cocain, *e. g.,* cannot raise the temperature.

The muscular paralysis *lowers the metabolism.* It is claimed that this diminution is far more conspicuous in the nitrogen, than in the carbon-metabolism.

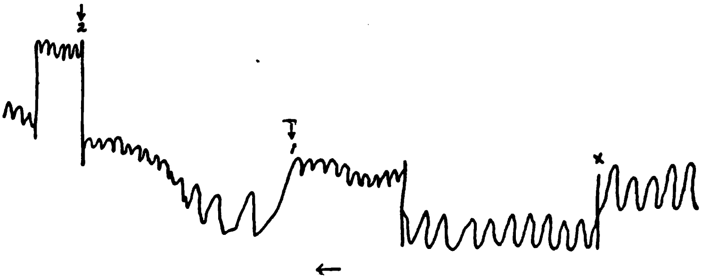

Fig. 58.— Curare. Carotid pressure, dog. The action begins at X. There is first a fall of blood pressure, due to vasoconstrictor depression; secondarily a rise and quickening, due to vagus depression. Stimulation of vagus $\updownarrow_{1}$ is effectual, but weak. Stimulation of sciatic $\updownarrow_{2}$ causes rise of pressure although the skeletal muscles are completely paralyzed.

2. Larger doses paralyze the nerve endings around the **sympathetic ganglia,** such as the vagus, vasomotor, salivary, pupillary, etc.

Stimulation of the vagus then usually only slows, but does not stop the heart. (Fig. 58.) At this stage the pupil is little affected; later it is dilated (paralysis of oculomotor?). The heart is quickened, after a slight primary slowing (nicotin-like stimulation?).

3. **Effects on the Circulation.**— If artificial respiration is maintained, the first effect of curare on the circulation consists in a *fall of blood-pressure,* due to peripheral vasomotor depression. This is soon accompanied by quickened heart beat, from depression of the vagus ganglia. The depression does not readily pass into paralysis, so that stimulation of the vagus or sciatic is still effective; indeed, the vasomotor reflexes may be increased, through the central action of the curare. These effects on the circulation do not appear to last as long as the effect on the voluntary muscles; they are indeed so small, that they do not seriously interfere with the employment of the drug in experiments. The main objection which may be urged against the latter is, that it does not produce sensory paralysis, whilst the absence

of struggling, etc., might cause the inexperienced operator to neglect a proper enforcement of other means of anesthesia.

An increase of *peristalsis* is often observed, but is probably due to asphyxia; so also are any changes in metabolism and largely the *glycosuria*.

4. **Central Nervous System.**— When curare is applied directly to the spinal cord it causes typical *strychnin convulsions*. With ordinary methods of administration these are masked by paralysis of the nerve endings. Certain samples, however, cause strychnin convulsions before the typical curare action appears.

IV. REASONS FOR INACTIVITY OF CURARE WHEN GIVEN BY STOMACH.

The effects of curare are obtained only if it is introduced under the skin or into the circulation, *not if introduced into the stomach*. The experiments on the administration of curare by the stomach have shown that —

1. It is not destroyed by the gastric juice, pancreatic juice, or saliva.

2. It passes very slowly through the walls of the stomach when the epithelium has been killed, and not at all if the epithelium is still living. (It will be remembered also that strychnin is not absorbed by the stomach in rabbits.)

3. It is to a large extent fixed or destroyed by the liver, for it is much less active when injected into the portal than into the jugular vein. It is also destroyed *in vitro* by ox-bile, and by bacteria.

In *frogs* the liver is the main agent in the disintoxication: in normal animals fifty times as much curare is required by mouth as hypodermically; the difference disappears completely if the liver is excised; digestion of curare with liver substance destroys its activity.

4. It is very rapidly excreted unchanged in the urine.

In *mammals* the inactivity of curare by the mouth is due partly to its destruction by the bile and bacteria; but mainly to the capacity for absorption being less than the capacity for its destruction or excretion. If the renal vessels are tied, poisoning occurs quite readily even when it is taken by the stomach. If very large doses are taken on an empty stomach, sufficient may be absorbed to cause symptoms.

V. TOXICOLOGY.

The toxicology of curare itself is at the present time of very little importance. The symptoms have been sufficiently discussed and consist of paralysis. In some cases in which it seems to have paralyzed the respiratory center before the muscles, it has given rise to asphyxial convulsions (or perhaps these were due to strychnin action).

Certain ptomains also exhibit a similar action.

The physiologic *treatment* would be the maintenance of artificial respiration until the poison has been excreted. Physostigmin may be used. The Indians use salt on the wound. This may be useful on account of the reflex stimulation which this causes when applied to an open surface.

VI. THERAPEUTICS.

Curare is a *laboratory drug*. It is of high importance in technic to immobilize an animal without producing any change in the circulation. It is also very useful when it is desired to investigate the properties of muscle exclusive of its nerve endings, etc.

Its *therapeutic application* is still largely experimental and not very promising. It has been suggested to combat the convulsions of strychnin, tetanus, and hydrophobia. It is certainly quite possible to suppress the spasmodic condition by sufficiently large doses. Unfortunately, however, it is impossible to secure this without at the same time paralyzing respiration. This latter may, theoretically, be counteracted by artificial respiration, but this prolonged manipulation is in itself injurious. On the other hand, minimal doses may be considered useless, and, indeed, as has been pointed out, even if the spasms could be suppressed without affecting the respiration, this would not be an ideal treatment for strychnin. In well-chosen cases, however, curare may be the means of saving life. Convulsions certainly tend to heighten fatigue and paralysis of the medullary centers, and if in a case in which the degree of poisoning just exceeded the lethal limit by a very little, a minimal amount of curare were injected, this might, perhaps, reduce the spasm sufficiently to turn the scale, or somewhat larger doses might be given which would require some, but not very much, artificial respiration. This has actually been done, and in desperate cases curare is worthy of a trial; but in addition to the other objections come the very uncertain quantitative effects. It would only be justified to work with tested samples, and these are very rarely accessible when needed.

Administration.— The drug should be given hypodermically, using per kilo. of patient $^1/_{10}$ the fatal dose determined per kilo. of dog; and being prepared for artificial respiration and physostigmin. Curarin, if pure, would give an exact substance, in the dose of 5 mg. hypodermically. The reliability of the alkaloid is, however, open to doubt.

(G) NICOTIN GROUP.

I. MEMBERS.

The group comprises *nicotin*, the active alkaloid of tobacco, and *piturin*, a very similar, if not identical, alkaloid, derived from *Duboisia Hopwoodii*, which is chewed by the natives of Australia as tobacco. The action of lobelin is also very similar.

Although nicotin forms the only important ingredient of tobacco or its smoke, its action, when used habitually, presents sufficient difference to entirely separate it from the acute action.

(A) Acute Action of Nicotin (and Piturin).

This bears the greatest resemblance to that of pilocarpin, with the following exceptions:

The effects upon the central nervous system are more marked and are mainly depressing.

In glands and unstriped muscle, it paralyzes the ganglia exclusively; its action upon the eye shows some differences.

It has a curare action on muscle endings.

II. SUMMARY OF ACTIONS.

1. Depression of the central nervous system, preceded by short stimulation.
2. A stimulation, and more lasting paralysis, of sympathetic ganglia in all situations.
3. A curare action upon skeletal muscle endings, also preceded by stimulation.

III. DETAILS OF ACTION.

1. Central Nervous System.— Stimulation, followed by depression, of the whole cerebrospinal axis, from above downward. The symptoms from large doses resemble those of asphyxia or hydrocyanic acid.[1]

The stimulation may be entirely absent, especially in large doses, so that the animal may drop dead almost instantaneously, without any other symptom. But this is not common.

The effects of small doses, such as are noticed in the first attempt at smoking, will be discussed later.

In mammals, moderate doses act mainly on the *hemispheres,* producing transitory excitement, followed by lasting depression, with violent headache. (In frogs, the action on the cerebral centers seems to be very small, for the effects are the same, whether the hemispheres are intact or removed.)

The action on the *medullary centers* is marked and violent; the *respiration* is at first increased, and then markedly depressed; paralysis of the respiratory center being the *cause of death.* The vagus and vasomotor centers are also first stimulated, and then paralyzed. The salivation and vomiting, which are so prominent with moderate nicotin intoxication, are probably also in part due to medullary stimulation.

The action on the *spinal cord* consists in strong stimulation of motor cells, producing convulsions, passage of feces and urine, etc. If the nicotin is applied to one part of the cord, the convulsions remain confined to the muscles innervated from this area (difference from strychnin, which acts on the sensory cells). The stimulation is followed by paralysis.

The *spinal ganglia* are not affected, even when a 1% solution of strychnin is applied directly to them.

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[1] Exercise 24.

The nicotin convulsions are not seated exclusively in the spinal cord, but involve the hind-brain and medulla as well. They are much weakened by anesthesia.

2. Peripheral Actions.— The peripheral effects of nicotin resemble those of pilocarpin; however, the action is confined to the ganglia; and the stimulation is succeeded promptly by paralysis.

From the situation of the nicotin actions, it follows that they can be removed by atropin or muscarin, but that the latter are quite unaffected by nicotin. The nicotin effects can be secured very efficiently by local application to the ganglia. If the preganglionic fibers have degenerated (7 to 26 days after section of the nerve), nicotin is still active, so that it must act upon the ganglion-cells themselves (Langley, 1901).

(*a*) **Action on the Circulation.**— The effects are shown in Fig. 59, and explained by Fig. 60. The heart is first greatly slowed, from central and ganglionic vagus stimulation. At the same time the blood-pressure begins to rise, from central vasomotor stimulation. Quite suddenly, the slow heart-beat is replaced by great quickening (paralysis of the vagus ganglia[1]). The blood pressure may be very high; but as the vasomotor ganglia become more and more depressed, the vessels become dilated and the pressure falls. The dilation can be plainly seen in the intestinal vessels or the rabbit's ear. The vasomotor ganglia are not readily paralyzed completely, so that direct or reflex stimulation, or a second injection of nicotin, again cause a short constriction. The heart muscle eventually wears out, mainly because of the lowered coronary pressure. The direct action of nicotin on the myocardium (as seen in excised hearts) seems to increase its irritability, so that it beats a longer time after death; but many experimenters differ from this view.

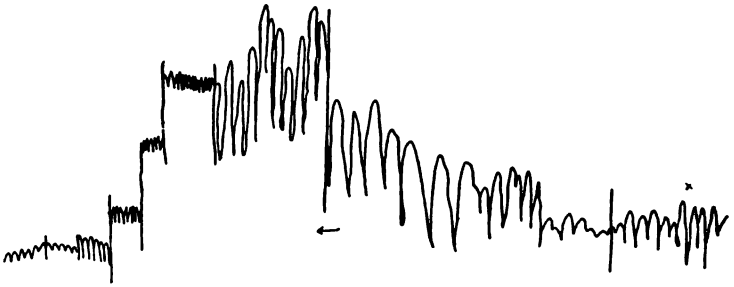

Fig. 59.— Nicotin. Carotid pressure, dog. The effect begins at X. The beats first become weaker; then very slow and strong (vagus stimulation), with progressive rise of blood pressure (vasoconstrictor stimulation). Suddenly they become very rapid and consequently smaller. The total work of the heart is unchanged and consequently the pressure remains high; but the vasoconstrictors becoming paralyzed, the pressure soon falls. Later the heart-muscle also becomes weakened, as shown by the small beats.

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[1] According to Kose (1905) this secondary acceleration also involves an accelerator stimulation, which passes finally into paralysis. These actions seem to be ganglionic.

(*b*) **Action on Unstriped Muscle.**— Nicotin acts on all unstriped muscle, paralyzing the ganglia after a brief stimulation; the tone of the muscles is lowered. This applies to the uterus, bladder, etc., but its principal action is on the *alimentary canal.* The peripheral effects may be concerned in the nausea and vomiting, but these are doubtless largely central. Nicotin also induces a violent *peristalsis,* and even tetanic contraction of the intestine. This is almost purely of peripheral origin, for it occurs also in excised intestine. It is immediately abolished by atropin. It must therefor be referred to a persistent stimulation of the ganglionic cells of Meissner's and Auerbach's plexus. At the same time, stimulation of the splanchnic and vagus becomes ineffective, so that the ganglia, which are intercalated between these nerves and the intestine, are paralyzed by the nicotin.

(*c*) The *pupil* shows both contraction and dilatation at different times, nicotin acting upon the ganglia of both the oculomotor and sympathetic fibers. There may even be a direct action upon the iris muscle. The effect is different in different animals: The dog and cat usually show dilatation; the rabbit first constriction and then dilatation.

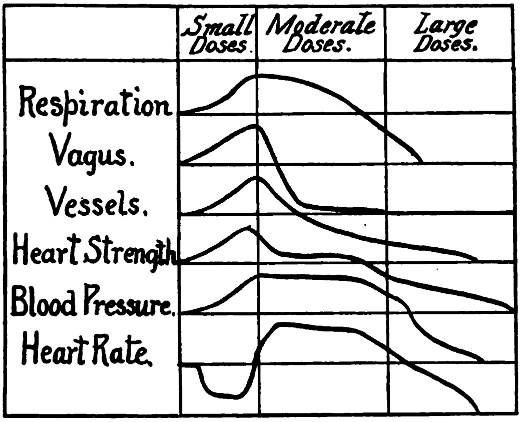

Fig. 60.— Diagram of the actions of nicotin.

(*d*) The general remarks already made suffice to define its action upon the *glands.*

(*e*) **Action on Skeletal Muscles.**[1]— These show at first *fibrillary twitchings,* which disappear after the section of the nerves, but are started again by short stimulation of the nerve or muscle. They are abolished by curare, and must hence have their seat in the endings as well as in the central nervous system. These twitchings are followed by typical curare paralysis.

In the milder stages this is shown by an equally strong, or stronger, current being required to obtain contraction when the stimulus is applied to the nerve than when it is placed on the muscle. In the normal preparation the opposite is the case.

The excitability and irritability of the muscle cells is also diminished by nicotin.

Nicotin shows a further agreement with curare in its effects upon the ganglia. Curare, of course, acts more upon muscle, nicotin upon ganglia.

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[1] Exercise 42.

Applied directly, strong nicotin solutions also paralyze the nerve-fibers.

In *lower animals* the degree of toxicity of nicotin is determined mainly by the development of their central nervous system.

Free nicotin is caustic on account of its alkalinity.

IV. TOXICOLOGY.

1. **Toxicity.**— Nicotin is one of the most fatal and rapid of poisons; the vapor arising from a glass rod moistened with it and brought near the beak of a small bird causes it to drop dead at once, and two drops placed on the gums of a dog may cause a similar result. The fatal dose for a man is about 60 mg.; of tobacco, about 2 Cm. It acts with a swiftness only equaled by hydrocyanic acid. And in view of the high nicotin-content of tobacco (one cigar contains a quantity of nicotin which would prove fatal to two persons, if directly injected into the circulation), also because of its popular distribution, it appears astonishing that fatal nicotin-poisoning is not more common; but just this wide distribution and knowledge of the drug form the safeguard, as also the marked taste.

Most cases of poisoning — outside of the slight ones from first attempts at smoking — have been produced by its medical application, especially by the laity; and since this has been largely abandoned, serious acute nicotin-poisoning has become very rare. It must be mentioned here that the application of tobacco to wounds or bruises is not without danger; since nicotin is volatile, it is absorbed from all surfaces, even from the intact skin, and fatal cases from this cause are recorded.

2. **Symptoms.**— In lighter cases, such as commonly occur in *smoking,* the peripheral actions predominate. There is first an increased flow of saliva, partly reflexly through the mechanical irritation of smoke, but mainly by direct stimulation of the ganglia through the nicotin. Nausea, vomiting, and diarrhea soon appear. The sweat-glands are also affected in a peculiar manner: There is a sensation of oncoming sweat, which does not actually break out. A sensation of exhaustion appears very early — partly as the result of nausea, but mainly as the first indication of central collapse action. Palpitation is also noted. Then come muscular incoordination, convulsions, and collapse.

The effects of poisoning with pure nicotin, which have been very carefully studied experimentally on *man,* bear the greatest resemblance to the above. After 1 to 4 mg. there were burning in the mouth, a scratching sensation in the pharynx, increased salivation, a sensation of heat spreading from the region of the stomach over the whole body; excitement with headache now appeared, then vertigo, confusion, disturbed vision and hearing, photophobia, dryness in mouth, cold extremities, nausea, vomiting, and diarrhea. Respiration quickened, but difficult. Pulse at first increased, then irregular. After forty-five minutes there was syncope, with clonic spasms. Recovery occurred, but a general depression persisted for three days.

3. The **treatment,** aside from the chemic, consists of coffee and other stimulants and in meeting the symptoms. Emetics will usually not be necessary.

4. The **postmortem appearances** are not characteristic, although large doses cause, in animals, anemia of the meninges and peculiar anatomic changes in the cortical nerve-cells. When taken by the mouth, there may be gastric and intestinal hyperemia, since nicotin is sufficiently alkaline to be somewhat caustic. The odor may furnish a valuable indication.

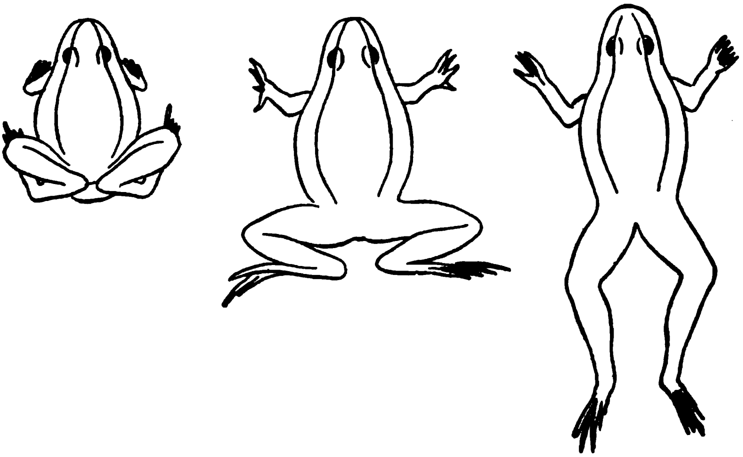

Fig. 61.— Nicotin. Successive positions of frog poisoned with 25 mg. nicotin.

The *proof* of the poison after its separation may be had by its odor and by obtaining its physiologic actions on frogs (see Exercise 42). The muscular tremors and the position which a frog assumes after nicotin are highly characteristic (Fig. 61). A control animal should, of course, be used.

The chemic tests are of no practical importance, since very similar reactions are given by coniin and by a ptomain.

The *excretion* of nicotin occurs mainly through the kidney, but also through the lungs and sweat. Nicotin is largely destroyed or fixed in the liver.

Nicotin is very *resistant to putrefaction,* and has been isolated from the decomposed bodies of animals three months after death.

(B) Habitual Nicotinism.— I. Chemistry of Tobacco-smoke.— The effects of tobacco-smoke are due almost purely to the nicotin contained in it. The erroneous statement has been widely disseminated that the smoke was free from nicotin. This view was based mainly upon theoretic deduction from the fact that the nicotin is present in tobacco in the form of a comparatively fixed salt. It was believed that the alkaloids in this form were burned by the heat of smoking. More exact recent researches have shown that under the conditions existing in smoking, the heat rises sufficiently high to set the nicotin free from its salt, yet not high enough to destroy it completely.

The effects of smoke upon frogs are precisely those of the nicotin contained in it. The drier the tobacco and the greater the heat, the less nicotin will escape destruction. Moist tobacco produces therefor the greater effects. In experiments something like 15 to 62% of the nicotin present in the tobacco are recovered from the smoke; but a greater part of this is exhaled or expectorated; in natural (intermittent) smoking, the aspirated smoke contains only a sixth of the nicotin; this explains why a cigar, containing, as has been said, nicotin sufficient to kill two men, were it directly injected, has so comparatively small an effect. But even smoking may have a fatal result if a sufficient quantity of tobacco is consumed. There are no data concerning the percentage of nicotin in chewing tobacco.

Tobacco smoke, however, does contain a number of *active substances other than nicotin,* especially the combustion products of the alkaloids and proteids: pyridin, picolin, quinolin; HCN and CO. The action of the first three bases resembles that of nicotin quite closely. (*Pyridin* is strongly irritant; it has been used as inhalation (10% by atomizer) in the treatment of asthma and fetid bronchitis.) Whilst all these substances are toxic, their quantity is too small to have any serious effect; *f. i.,* the HCN in the smoke of a cigar amounts only to 0.02 to 0.5 mg. However, if a large number of persons smoke in a confined atmosphere, the carbon monoxid in the air of the room may rise to a dangerous degree. The aromatic essential oils, which give the flavor to tobacco, are practically inactive.

Arsenic is sometimes present in harmful quantities when Paris-green has been used on the plant as an insecticide.

However, the oils and bases aid the nicotin to produce certain *local effects:* the biting sensation on the tongue. noted especially when the smoke is concentrated on one point, as in pipe-smoking. This constant local irritation also seems to favor the development of epithelioma. There is also a more general irritation of the mucous membrane of the mouth, throat, and pharynx, leading to catarrh and hoarseness. But these results follow only when the quantity consumed is very large or the smoker specially disposed.

II. General Effects.— The question of the effects of smoking has been largely discussed with a rather unscientific extremeness, some contending that it is entirely harmless when moderately used; whereas, on the other hand, an enthusiastic French writer has gone so far as to attribute the defeat of his nation in the war of 1870 to the prevalence of cigarette smoking. Of the two views, the former would seem to come nearest the truth if the stress is laid upon the word "moderate."

Since, next to caffein, nicotin is the alkaloid most widely used, an impartial discussion of this question is important.

1. *Tolerance and Habituation.*— The quantitative effects of nicotin vary considerably in different persons. These variations can also be observed on animals: *young individuals* are much more readily poisoned than adults. It is a familiar fact that a considerable degree of tolerance to nicotin is readily acquired by its repeated use. This may also be observed in animals (Hatcher, 1904); it would seem that the tolerance is much greater toward the usual effect of small doses, than toward toxic doses. The serum of habituated animals does not protect others from the intoxication.

It is also a common experience that the degree of this tolerance presents great individual variations: Whilst one person may become easily accustomed to its use, another may be entirely unable to overcome the trial-stage, and others must be careful not to exceed a very limited amount. This variability depends not only on differences in the susceptibility of the individual, but also upon the manner of using the drug — whether or not the smoke is deeply inhaled, the saliva expectorated, etc.

The habituation is usually very rapid, and nicotin loses, in moderate doses, all its usual acute effects.

When this immunity has once been acquired, the continued use of tobacco within a certain individual limit produces absolutely no unpleasant symptoms; but if the limit be at any time sufficiently exceeded, the symptoms of chronic poisoning, presently to be discussed, arise. After a long time, some twenty years, these symptoms may also, but rarely, occur in those who have always kept within bounds.

Once the immunity to the usual acute action of nicotin has been acquired, its use by smoking, chewing, or snuffing brings with it a certain pleasant sensation, which appears to be entirely wanting with the beginner. This is somewhat difficult to define. There appears to be a certain repose, which, whilst it neither directly aids nor hinders the psychic processes, leaves the mind free, and in general raises the user's enjoyment of other pleasures, or lessens his annoyance at the opposite. The experience of recent campaigns appears to show that the use of tobacco enables soldiers to endure greater hardship.

How much of these effects is due to nicotin, how much to other factors, we cannot say. It is certain that the nicotin strength of the tobacco is not the determining feature of this action — rather the aroma. Smoking in the dark does not give as much enjoyment; and simply holding an unlighted cigar in the mouth, the chewing of other objects, etc., give similar, though much weaker, sensations. The truth would seem to be that it depends upon a reflex stimulation, from the mucous membrane of the mouth, nose, etc., in which the nicotin plays a part; and with this may be associated a direct action of the nicotin upon the central nervous system, at once stimulating and depressing.

Aliprandi and Fornaroli (1905) claim that tobacco-chewing causes a distinct constriction of the cerebral vessels.

2. *Chronic Intoxication.*— The symptoms from this are quite va-

riable, but may be briefly stated as: ***Functional arhythmia of the heart, digestive disturbances, depression of various parts of the central nervous system, and neuralgias.***

The first symptom to be noticed, the first warning, is occasional ***palpitation,*** the pulse-rate being at first quickened by depression of the vagus ganglia; if the nicotin is continued, this becomes quite persistent, but stops upon withdrawal; in advanced cases it may be necessary to continue the abstinence as long as six months or more. In the more advanced cases, the pulse may also be slowed. ***Arhythmia*** is always present. In still graver cases, the quickening and arhythmia may be extreme and approach the delirium cordis. Sudden ***syncope*** also occurs. ***Respiratory distress*** naturally accompanies the marked cardiac phenomena. The effects upon the heart are ***functional,*** not organic. Angina pectoris is so rare in these subjects that it must be attributed to causes other than the nicotin. On the other hand, ***arteriosclerosis*** appears to be favored by it.

The symptoms next in order are probably those arising from the ***alimentary canal,*** and depending upon the continued irritant action of the nicotin. These are: Loss of appetite, then dyspepsia and chronic intestinal catarrh, shown by alternating constipation and diarrhea. (With moderate smoking the nicotin seems rather to have a tendency to keep the bowels regular.) These conditions lead to emaciation and anemia. A direct action upon the blood may also have a part in this; the continued administration of nicotin to animals leading to diminution of red corpuscles, and increase of leucocytes. It is also claimed that it diminishes the oxygenating power of hemoglobin. The nitrogen excretion is rather more diminished than the assimilation, so that there may be a gain in body-nitrogen.

Paralyzing effects upon the ***central nervous system*** become apparent; these are rarely of a serious nature. The ***psychic functions*** show a slowness and want of energy. Anxiousness and insomnia are quite frequent. There is a general muscular debility, tremors, and want of control over movements. The reflexes are heightened. Vertigo and a tabetic condition may set in. There is then an increase of excitability in the sensory and pain areas, and consequently headache and neuralgias; but the latter are in part due to referred pain from the cardiac disturbances. They are often early and quite characteristic, and take the form of pain and ***hyperesthesia*** in the precordial region, left nipple, and ulnar surface of left arm.

The ***special senses,*** and especially ***vision,*** are also affected. The latter becomes dim and the accommodation faulty; miosis is frequent. These conditions are at first readily removed by withdrawal, but in advanced cases they may lead to an atrophy of the optic nerve and retinal ganglion cells.

Transitory aphasia is also an occasional phenomenon, and so is transitory albuminuria, the latter due to irritation of the kidneys by the excreted nicotin.

Of other effects which have been attributed to nicotin, but with insufficient cause, may be mentioned: impotence, epilepsy, and insanity (G. W. Jacoby, 1898).

3. Treatment.— It will be seen that the catalogue of injurious actions to be charged against the abuse of this drug is sufficiently large; but on the other hand, it must be noted that these are absent with moderate use, and can be abolished if the use of the drug is promptly limited on their first appearance. Actual withdrawal is not always necessary. Limitation in quantity, the use of tobacco poor in nicotin, sufficient expectoration, and the avoidance of deep inhalation of the smoke, are often sufficient. Quick total withdrawal does not lead to abstinence symptoms, as with morphin (except possibly in some especially neurotic subjects), although it may disturb the function of the bowels for a few days. The principal point in the treatment is to keep the thought of the patient off the topic of tobacco, and to supply the accustomed stimulus to the mouth in some other manner, as by chewing ginger or gentian.

The use of tobacco must, of course, be avoided in pathologic conditions in which there are special contraindications to it — in heart disease, dyspepsia, inflammation of the respiratory tract, etc.

Tabacum (Tobacco).— "The commercial dried leaves of Nicotiana Tabacum, Linné (N. O. Solanaceæ." An annual plant, probably indigenous in tropical America, and now cultivated in most parts of the world. The annual production of the world is estimated at a million tons (1,000,000,000 kilograms). Other species also contain the nicotin. The plant was introduced into Europe shortly after the discovery of America. Its use by smoking was practised by the natives at the time of Columbus.

The important constituents are nicotin, which is also present to a less extent in all other parts of the plant, and a volatile oil developed in drying and "sweating." The percentage of nicotin varies between one and eight per cent.: In Havana and Maryland, 1.5 to 3; Virginia and Kentucky, 6 to 8; South American, 2 to 6; German, 1.5 to 3.[1] Three other alkaloids have also been announced to exist in small amount in tobacco.

The cultivation of tobacco requires a great deal of care. The plants are first grown in seed beds, and later transplanted into fields. Only particular climatic and soil conditions will give good tobacco, and even the fertilizers must be carefully selected, since they will have an effect upon the ash. The variety of the tobacco depends largely upon the soil; a light sandy soil giving thin, light-colored wrapper leaves, and a heavy rich clay giving dark, thick fillers. But often wrappers and fillers are taken from the same plant. The plants are "topped" so as not to produce seed, and when the leaves are ripe — *i. e.*, when they begin to change color, become spotted and break easily — they are cut. These fresh leaves are practically odorless, the odor becoming developed in wilting, and especially by fermentation through enzymes. The substances which give rise to the ethereal oils are little known — they appear to be of the nature of glucosids. These oils are present in only very small quantities — 100 kg. of Brazilian tobacco having yielded only about 20 Gm. Extreme dilution does not destroy their aroma. The quantity of these oils varies often, but not always, with the nicotin-content.

The development of aroma is not the only step necessary in the preparation; it is quite essential to destroy substances present in the leaves — mainly of proteid and fatty nature — which would give the smoke a very unpleasant odor. This is done by "curing." Curing is also a fermentation, having for its object the destruction of these proteid substances by bacterial action. It is accomplished essentially by piling the tobacco in a warm, moist place to secure the conditions favorable to the action of the bacteria. It is often aided by dipping the leaves into saccharine solutions (molasses, cider, etc.). These are often flavored ("pituring") with anise, cinnamon, etc. But few tobaccos, naturally poor in proteids, such as some Havana and Asiatic varieties, can be used without this curing, which is an undesirable feature, since some of the aroma and nicotin are also lost in the process — the more, the longer it is carried on. To restore this, the leaves are sometimes soaked in infusions of tobacco stems, etc.

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[1] Cigars (Austrian) contain 1.3 to 4% of nicotin; the percentage in cigarettes and pipe-tobacco is similar.

The cured tobacco has only a slight odor; the real aroma is brought out in the "sweating" — a later fermentation, taking place also in stored tobacco. In this process one-fourth to one-third of the nicotin disappears.

The dried leaves were formerly official; if used, an infusion may be made.

(H) MINOR MEMBERS OF THE SERIES.

1. CONIUM.

1. Composition.— Conium (Water-hemlock) contains a *number of alkaloids,* viz., coniin, methyl-coniin, conicein, and conhydrin.

They *differ mainly in the strength of their action.*

The commercial coniin consists of a mixture of the above, and as this alone has been employed on man, the following remarks apply to this mixture. As these alkaloids decompose very rapidly, the commercial preparations are often entirely inactive. The hydrobromid is the most stable. A very similar alkaloid is present in some species of Lupinus.

II. Summary of Actions.— Coniin bears a very *close resemblance to nicotin* in its physical and chemic characters, in its composition and actions. The latter differ in a more pronounced paralysis of the central nervous system and of the endings in striped muscle.

(The mother-substance, piperidin, has a similar but weaker action.)

III. Details of Action.— I. Peripheral Organs.— Coniin stands midway between curare and nicotin, paralyzing both motor endings and ganglia, and forming with the other members a series running: Curare, coniin, gelseminin, spartein, nicotin; the action on the motor endings predominating with the former; that on the ganglia with the latter.

Its action on the pupil, heart, blood-vessels, circulation, alimentary canal, glands, etc., is precisely as with nicotin, only weaker.

The muscle substance is not affected. Applied directly to the skin it diminishes sensation.

2. In its action upon the **central nervous system,** the resemblance is also very great, but the stimulation is still less, and the *depression* is so strong that it forms the most prominent feature of poisoning in man. *Consciousness* is little or not at all affected, the main symptoms referring to the motor system, and these are very characteristic. The paralysis is *ascending,* beginning with the lower extremities, and finally reaching the *tongue,* so that the patient may be unable to speak whilst his intellect is not yet disturbed.

This ascending paralysis has been explained by a lowered *conductivity* of the cord to impulses coming from the brain, the path being blocked at first only to those impulses which have a long way to travel.

The *excitability* of the cord is not decreased, however, so that *convulsions* may appear. These can occur only in mammals, since the curare action is an early feature in the frog; and this undoubtedly plays its part also in the paralysis in man.

Depression of the medullary centers is also a prominent feature, and death occurs by *paralysis of respiration.* This is also due in part to the curare action.

IV. Toxicology.— Coniin is *much less toxic than nicotin;* 85 mg. do not produce as violent symptoms as 4 mg. of the latter; but this may be partly due to the fact that the pure alkaloid was not employed. The *symptoms* are very characteristic, and they have been so well described in Plato's classic rendering of the death of Socrates, that no difficulty is experienced in recognizing the substance used in the poisoning of this philosopher. The description is so accurate that it may well serve to represent the usual *symptoms.*

After drinking the poison, "He [Socrates] went about, and as he noticed that his thighs became heavy, he laid down on his back, as the man directed. The latter — the one who had given him the poison — touched him from time to time, and investigated his feet and thighs. Then he pressed his foot strongly, and asked whether he could feel it; he answered, No. Then he tried the knees, and so went higher and higher, and showed us how he gradually became cold and stiff. Then he touched him once more, and said, when it came to the heart, then he would be dead. Now almost everything from the abdomen down was cold," and Socrates then spoke his last words to his friends, but was unable to answer further questions. He had a short spasm and was dead.

From the quick action, it is supposed that he must have been given the expressed juice of the root, and it is very probable that the Greeks commonly used their poisons in this form.

Coniin may be *recognized* by its characteristic narcotic odor. Like nicotin, it is liquid, colorless, becoming brown in air. The test consists in the curare action on injection in the frog. The chemic reactions are of little value, since they resemble nicotin very closely, and are given by a ptomain.

2. LOBELIN.

Lobelin, the alkaloid of Lobelia inflata, has an action essentially identical with nicotin (Edmunds, 1904).

Small doses stimulate, large doses paralyze, the respiratory center. The vagus endings in bronchial muscle are also depressed. Small doses taken continuously cause a persistent quickening of the pulse.

Anagyris fœtida, a leguminous plant indigenous to the shores of the Mediterranean, and there used as a substitute for senna, contains an alkaloid, anagyrin, whose pharmacologic actions resemble those of lobelin in many respects.

3. GELSEMININ.

Gelseminin, the active alkaloid of gelsemium, produces *effects in general almost identical with those of coniin.* Its *depressing action* on the central nervous system is more marked than that of the latter, so that the central paralysis precedes the peripheral even in frogs.

It has a very decided *mydriatic effect* upon the pupil, especially on local application. This is believed by some to be due to paralysis of the oculomotor endings after the manner of atropin; but the question cannot be considered as definitely settled. The mydriasis lasts from twelve to seventeen hours.

(*Gelsemin,* another alkaloid, has an extremely weak strychnin action. It increases the spinal reflexes, but abolishes voluntary movements. The commercial "Gelsemin" is a mixture of both alkaloids, owing its activity to Gelseminin.)

4. SPARTEIN.

The last member of this series is spartein, a liquid, oxygen-free alkaloid existing with a neutral principle, scoparin, in the *broom plant.*

Spartein, while showing a close general resemblance to coniin, presents some important *differences:*

The *central actions are weaker,* the *peripheral stronger.*

The most important action of spartein is that on the heart. By stimulation of the vagus mechanism, and direct depression of the muscle, the *cardiac contractions are slowed and weakened.* (Spartein cannot, therefore, be classed with digitalis, as is sometimes done; for the latter, although it slows the heart, strengthens the contractions.) The *blood pressure is usually lowered* when the drug is taken by the mouth, since the depression of the heart is more than the constriction of the vessels which it also produces.

The diuretic action of broom-top is not due to the spartein, but to the scoparin.

(I) PHYSOSTIGMIN (ESERIN).

The peripheral actions of physostigmin are directly antagonistic to atropin, and correspond therefore to those of pilocarpin and muscarin; but there is reason to believe that it acts more peripherally than any of these alkaloids, *i. e.,* that its action extends also to the cells themselves.

I. SUMMARY OF ACTIONS.

1. Stimulation of endings and cells in all muscles (striped, unstriped and cardiac), and in glands.

The action on the pupil (miosis) and on the intestine is especially powerful.

2. Fleeting stimulation and pronounced depression of the central nervous system.

II. DETAILS OF ACTIONS.

1. The Eye.[1]— Physostigmin, whether applied locally or taken internally, causes constriction of the pupils, spasm of accommodation, and lowering of the intraocular pressure. These actions are due mainly to stimulation of the oculomotor endings and of the muscles of the iris and ciliary body. The effects of physostigmin can be removed by the application of atropin, and vice versa; but this requires much larger doses than does a normal eye.

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[1] Exercise 54.

The miosis is not as pronounced as with muscarin, probably because the opposing radial muscles are also stimulated. The action, however, is mainly on the endings, for the effect is much less when these endings are degenerated. A simultaneous stimulation of the oculo-motor center cannot be excluded, but is not probable.

2. The contraction of the **cardiac muscle** is slowed but strengthened. This slowing occurs even after atropin, showing that its cause is at least largely independent of the vagus. The amplitude is first increased, then diminished. In frogs, physostigmin causes the heart to resume its beat after this has been stopped by muscarin; this is the best proof that physostigmin stimulates the cardiac muscle directly. There is no conclusive evidence that it exerts this stimulant action on the mammalian heart. Strong doses cause systolic standstill of the frog's heart.

The *blood-pressure* rises at first; this rise depends only in small part upon the strengthened heart, since this is largely counteracted by the slowing. Nor is it due to stimulation of the vasomotor center, direct or reflexly through convulsions, since it occurs in curarized or chloralized animals. Its cause lies in the *direct peripheral stimulation of the arterioles,* aided by the displacement of blood from the abdominal viscera, consequent on the violent peristalsis. According to Dixon (1903), the vasoconstriction is due to stimulation of the endings, not of the arterial muscle; for it does not occur after apocodein, which paralyses the endings.

The rise of blood pressure is followed, with large doses, by a severe drop, due to paralysis of the vasomotor center and the weakened heart.

3. By stimulation of the **unstriped muscle** it causes violent peristalsis, vomiting, and contraction of bladder, spleen, uterus, arterioles, and bronchial muscles.

The stimulation of the **intestine**[1] results in fixed tetanic contraction rings, rather than in regular peristalsis. This effect may be produced after atropin; but it can also be removed by large doses of this drug, so that it is not muscular, but due to stimulation of the endings. The same holds true of its action on other unstriped muscle.

4. The **glands,** especially the salivary, mucous, lachrymal, and sweat-glands and pancreas, are stimulated by physostigmin; and since it acts promptly after atropin, its action is probably partly on the gland-cells themselves. The increase of secretion is, however, not nearly so marked as with the other members of the series, since it is *counteracted by the constriction of the blood-vessels.*

5. **Striped Muscle.**— In mammals these exhibit peculiar fascicular contractions, persisting after the section of the nerve. They are diminished, but not abolished, by moderate doses of curare, showing that the stimulation resides only partly in the endings; and the view that the muscle-fiber is *stimulated in part directly* is also supported by the fact that its working power and irritability are increased. Physostigmin also removes the paralyzing effects of curare, so that stimulation of the nerve again becomes effective (Rothberger, 1901).[2]

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[1] Exercise 67.

[2] Exercise 42.

6. On the **central nervous system,** its action is rapidly paralyzing, *beginning,* at least in man in the *lower portions,* so that *consciousness is preserved* to the end. The *respiration* is at first increased; this is due largely to stimulation of the afferent endings of the vagi; for the quickening is much less after the vagi have been cut. There are also other evidences of stimulation—excitement, etc.—but these have been considered *secondary to respiratory paralysis,* the central actions of the alkaloid being mainly depressing. Dyspnea is a marked symptom, due to paralysis of the respiratory center and spasm of the bronchial muscles. Asphyxia forms the *cause of death.*

III. TOXICOLOGY.

The **symptoms** of physostigmin poisoning consist of: nausea, vomiting, and diarrhea; salivation, lachrymation, and sweating; palpitation with slowed pulse; miosis; excitement and dyspnea; weakness with muscular twitchings; convulsions. Death by paralysis of respiration under general collapse, the reflexes persisting to the end.

Treatment.— General alkaloidal. Physiologic antidotes: atropin and strychnin.

Proof.— Its physiologic action upon the eye is among the most characteristic.

As physostigmin is very readily decomposed by light (solutions acquiring a reddish color and losing much of their activity), its search must be conducted, as far as possible, in the dark, and the employment of heat should also be minimized.

PISCIDIA.

The bark of *Piscidia Erythrina* (*Jamaica Dogwood,* Papilionaceæ, West Indies) contains an amorphous, neutral, non-glucosidal principle, *Piscidein,* $C_{14}H_{15}O_4$, insoluble in water, soluble in alcohol. According to Vejux-Tyrode and Nelson (1905) this acts very similarly to physostigmin. It produces a general paralysis, which has led to its use as a fish-poison. The animals still respond to direct stimulation of the spinal cord, so that the paralyzing action must be on the sensory tracts. The respiratory and vasomotor centers succumb early without preceding stimulation. Consciousness is not affected until collapse occurs. Peripherally, the poison stimulates the smooth muscle of the intestine and bladder. There is no indication of narcotic action (which was formerly claimed). The drug does not seem to be therapeutically useful. The *dose* is given as 1 to 3 Gm. (15 to 45 grains).

(K) RESUME OF THE SERIES.

I. METHODS OF STUDYING.[1]

1. Localization of the Actions.— A *paralysis* is localized by stimulating above and below the affected portion; the latter is effective, the former is not.

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[1] Exercise 37.

A *stimulation* is localized by paralyzing above and below; the latter stops it, the former does not.

It must be remembered that a slight degree of paralysis may be overcome by a strong stimulation; also, that a paralysis *above* a stimulation may appear to lessen the latter, if this has been previously supported by normal central tonic impulses.

Stimulation or paralysis may be applied: (1) *electrically* or by section.

Heart	Cardiac vagus: trunk, postganglionic (sinus). Cardiac accelerator: trunk. Cardiac muscle.
Eye, Dilator Mechanism...	Cervical sympathetic (preganglionic). Superior cervical sympathetic ganglion. Long ciliary nerve (postganglionic). Radial muscle.
Eye, Constrictor Mechanism...	Oculomotor nerve (preganglionic). Ciliary ganglion. Short ciliary nerve (postganglionic). Sphincter muscle.
Submaxillary..	Chorda tympani and cervical sympathetic (preganglionic). Hilus (postganglionic). Cells.

2. *Drugs* (in appropriate doses).

Paralysis	Cells: apomorphin, copper. Nerve endings: atropin. Nerve-ganglia: coniin, nicotin.
Stimulation ...	Cells: Physostigmin. Nerve endings: Muscarin. Nerve-ganglia: Nicotin.

It must be remembered that the action of the different members is not marked off absolutely sharply. They all stimulate and then paralyze, and they all affect every portion of the nerve-ganglion-ending-cell chain.

II. MAIN PERIPHERAL ACTIONS OF DIFFERENT MEMBERS OF SERIES.

Atropin: Paralysis of endings in glands and unstriped muscle. Strong solutions: Stimulation, then paralysis, of muscle-fibers.

Muscarin: Stimulation of endings in glands and unstriped muscle.

Physostigmin: Stimulation of endings and cells.

Pilocarpin: Long stimulation of ganglia and endings, followed by very late paralysis.

Nicotin, Gelseminin, Lobelin, Spartein: Long stimulation of ganglia, followed more quickly by paralysis.

Curarin, Coniin: Paralysis of ganglia (and muscle-nerve endings).

III. ACTION ON PARTICULAR STRUCTURES.

1. **Heart: Vagus Mechanism.— (a) Ganglia:** *Nicotin, pilocarpin, lobelin, gelseminin,* and *spartein* produce stimulation followed by paralysis. *Curarin, coniin,* and *cocain* produce almost pure paralysis.

(b) Postganglionic Fibers (Endings of Vagus): Stimulated by *muscarin* (*pilocarpin, physostigmin*), *thyroiodin,* [sodium phosphate, digitalis, etc.]. Paralyzed by *atropin, sodium iodid.*

(c) Muscle-fiber: Stimulated, then paralyzed, by *atropin;* almost pure stimulation by *physostigmin* (veratrin, digitalis, camphor, etc.); almost pure paralysis by apomorphin or copper salt.

2. **Pupils.— (a) Stimulation of Dilator (Sympathetic) Endings and Ganglia:** Cocain.

(b) Paralysis of Constrictor (Oculomotor) Endings: *Atropin* (*gelseminin?*).

(c) Stimulation of Constrictor (Oculomotor) Endings: *Physostigmin, muscarin.*

The other members of the series may act upon either mechanism.

3. **Glands.— (a) Ganglia:** Stimulated, then paralyzed, by pilocarpin and nicotin. In case of former, paralysis comes very late.

(b) Endings: Stimulated by muscarin, pilocarpin, physostigmin. Paralyzed by atropin.

IV. EFFECT OF MODERATE DOSES UPON:

1. **Blood pressure.**

Atropin: Small and variable.

Nicotin, Pilocarpin: Rise with slowing. Former mainly stimulation of vasomotor ganglia, latter of vagus. Later quickening with further rise, then fall.

Curare, Conium: Mainly fall through vasomotor paralysis — both central and peripheral.

TABLE X.—DRUGS ACTING PERIPHERALLY UPON GLANDS AND UNSTRIPED AND CARDIAC MUSCLES.

	CENTRAL NERVOUS SYSTEM.	GANGLIA.	Peripheral Endings in Glands and Unstriped and Cardiac Muscles.	Direct Action on Cardiac and Unstriped Muscles.	ENDINGS IN SKELETAL MUSCLES.	SECRETIONS.	HEART.	PUPIL.	PERISTALSIS.
Tropeins	Stimulation, then depression.	None.	Paralyze.	Short stimulation and in large doses paralysis.	Slight curare.	Diminished.	Quickened.	Dilated.	Diminished.
Muscarin	Stimulation, then depression.	None.	Stimulates.	Large doses paralyze.	Curare action.	Increased.	Slowed.	Constricted.	Increased.
Curare	Stimulation, then depression.	Short stimulation, then paralysis.	None.	None.	Paralyzes.	Diminished.	Quickened.	Constricted.	Diminished.
Lobelin ..... Pilocarpin ... Nicotin	Mainly depressing.	Short stimulation, then paralysis.	Pilocarpin produces stimulation, others no effect.	Like atropin.	Stimulate, then paralyze.	Increased.	Slowed, then quickened.	Variable.	Increased.
Coniin ...... Gelseminin Spartein	Mainly depressing.	Short stimulation, then paralysis.	None.	Like atropin.	Stimulate, then paralyze.	Increased.	Spartein permanently slowed.	Dilatation.	Increased.
Physostigmin.	Mainly depressing.	None.	Stimulates.	Stimulation.	Stimulate.	Increased.	Slowed.	Constricted.	Increased.
Apomorphin .	Mainly stimulation.	None.	None.	Depression.	None.	(Increased through nausea.)	Slowed.	None.	Diminished.

Physostigmin: First rise, but mainly fall through paralysis of central nervous system.

2. Heart-rate.

Atropin, Curarin, Coniin, Cocain: Quickens.
Pilocarpin, Nicotin: First slowed, then quickened.
Physostigmin, Spartein: Slowed.

3. Pupil.

Dilated: Atropin, cocain, euphthalmin, gelseminin, nicotin, coniin.
Constricted: Muscarin, physostigmin, pilocarpin.

4. Peristalsis.

Arrested by atropin, quickened by all the others.

(L) THERAPEUTICS OF PILOCARPIN SERIES.

Of the actions of this series, the peripheral effects of *pilocarpin* and *physostigmin* are almost the only ones which attain to a practical importance. Nicotin, as well as the other members, possesses few, if any, advantages over these, and on the other hand, a number of *other undesired* and more or less violent *actions,* especially the depression of the central nervous system, the irritant action on the alimentary canal, and the cardiac disturbances. These are much less marked in the case of pilocarpin, so that they may be entirely avoided in ordinary doses. But it has been attempted to use some of the *special actions* of the others:

1. **Coniin** has a depressant action on the central nervous system and a curare effect upon muscle. This would justify its employment in *spasmodic conditions,* such as strychnin-poisoning or any other tetanus, in chorea, whooping-cough, torticollis, etc. It would possess the advantage over curare that it acts on the seat of the disease — centrally — as well as peripherally. Its usefulness is much lessened by the uncertain strength and action of its preparations, due to their ready decomposition. The hydrobromid deserves preference.

2. **Lobelia** has been used as an emetic, but it possesses no advantage over apomorphin or emetin, is more depressant, unreliable, and if vomiting does not occur, it produces very violent symptoms. The preparations also vary much in activity.

3. **Gelsemium** is used both locally and internally as a mydriatic, but is inferior to atropin.

4. Spartein has often been tried, to raise the work of the *heart* and produce moderate slowing. It does the latter, but not the former, according to experimental and the bulk of clinical evidence; it is therefore of no value in heart disease, or, at most, only in the same cases as aconite. Doses of 0.01 Gm. ($\frac{1}{6}$ grain) are specific in some cases of asthma. The broom plant contains another principle, scoparin, which makes it of value as a diuretic in fevers, etc. This will be considered later.

5. Physostigmin has been tried as a *nervous depressant* in epilepsy, chorea, tetanus, etc. The results have not been satisfactory, perhaps because a sufficient dose cannot be given without bringing on respiratory disorder.

The *diaphoretic action* cannot be obtained sufficiently pure to be useful. Its powerful effect on the *intestine* has been utilized to open the bowels after operating (to 2 mg. = $\frac{1}{30}$ gr.) and in intestinal atony; but it is somewhat dangerous.

Its usefulness is mainly limited to **ophthalmologic practice.**

The *lowering of intraocular pressure* makes it *the* remedy in *glaucoma;* and the miosis is used in alternation with atropin to break up *adhesions of the iris to the lens* — a condition now generally treated by operation, however. It may be used to counteract the *paralysis of accommodation following atropin.*

It is used for its effects on the eye locally in ½% *solution* (of the salicylate). The miosis begins in five to fifteen minutes, reaches its maximum in half an hour, and passes off for the most part in an hour, but little effect remaining after this time. The effect upon accommodation begins somewhat later and is more lasting.

6. With **pilocarpin** the *stimulation of the salivary and sweat glands* is the most prominent and among the earliest actions, so that it may be obtained almost free from any of the other effects. The alkaloid is to be preferred. The preparations of the crude drug remain longer in the alimentary canal and have therefore more opportunity to exert the objectionable action here. They are also of very uncertain strength.

The increased secretion leads first to a *removal of liquid* from the body, and with this, of *waste and toxic products* of all kinds. The former indicates it in all conditions where there is an *accumulation of fluid,* especially when of renal origin; in dropsy, effusion into retina or brain, etc. It not only removes the accumulated fluid, but also *relieves the kidneys* of a part of their work. The removal of fluid pressing upon the veins, etc., leads to an *improvement in the general circulation,* and thus removes also the congestion of the kidneys; in consequence—and not by any direct action—the *quantity of urine* is increased. Its main indication in dropsy, then, is in that of renal origin, not nearly so much when the disease is cardiac; for here its tendency to depression of the heart and circulation in general vitiates its beneficial effects.

The removal of toxic products from the body makes it useful in *uremia,* in *chronic opium-poisoning,* etc.

So much for its effects upon secretion as a whole.

The increase in sweat, saliva, mucus (and milk), are in particular utilized practically. For its use as a sudorific see below. The increased action of the *sweat glands* brings with it an increased **circulation in the skin,** and this secondarily increases the *growth of the hair,* and, it is claimed, also turns it to a darker color. It may be used for the former purpose. Its **sialogogue action**[1] is employed against poisons which suppress this secretion, as those of the atropin group and certain meat-poisons. The increased secretion of *mucus* makes it useful in all cases of *dry cough* (see Chap. XXIII, C), and this action is aided by its nauseant properties. It may also result in loosening false membrane in *croupous conditions,* and be the means of saving life. This liquefying action on the mucus, as well as their action on the respiratory center, has determined the use of pilocarpin, tobacco, and lobelia in *asthma.* Pilocarpin should be avoided in all inflammatory conditions of the lungs, for fear of pulmonary edema. *Its dose should never exceed* 0.01 *Gm.* ($\frac{1}{6}$ *grain*). Similarly the increase of biliary mucus, produced by pilocarpin, facilitates the passage of *gall-stones.*

An increase in the secretion of milk may perhaps be considered doubtful.

Its *nauseant action,* and that on *peristalsis,* could possibly be utilized therapeutically; but it is inferior in these respects to other remedies (see Chapters XIV, C; and XXXII), and these form rather *unpleasant side-actions,* partly directly and partly by the general depression which they produce.

The *slowing of the heart* produced by the members of this series is of no practical importance, since it cannot be obtained sufficiently pure. The constriction of the *pupil* and lessening of intraocular tension have caused pilocarpin to be used as a *substitute for physostigmin* in glaucoma. It has no advantage over the latter drug, its action being shorter and less complete. A 2% solution is employed locally.

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[1] Sialogogues (measures which increase flow of saliva) may be divided, according to their action, into:
(a) Those which stimulate the nervous mechanism of the salivary glands directly: Pilocarpin, physostigmin, etc.
(b) Those which stimulate the nervous mechanism of the salivary glands reflexly: Acids, sapid substances, alcohol, local irritants (saponins), nauseants.
(c) Those which irritate the gland cells: Mercury, iodids, ipecac, etc.

The action on the *uterus* may result in abortion, but cannot be used in practice, since the doses required for its action on this organ are dangerous.

Lastly, pilocarpin forms the physiologic *antidote to atropin* and certain snake-venoms (rattlesnake).

(M) DIAPHORETICS.

Diaphoretics (sudorifics or hydrotics) are remedies which increase the secretion of sweat, an object which may be attained in the following manner:

(*A*) *By affecting the circulation in the skin:*

Locally:		1. Local irritation.
Systemically:	Indirectly:	2. Rise of general blood pressure if cutaneous vessels are not simultaneously constricted.[1]
	Directly:	3. Stimulation, direct or reflex, of the central dilator mechanism of the cutaneous vessels, or,
		4. Paralysis of their vasoconstrictor mechanism.

(*B*) *By directly increasing the secretory activity of the cells of the sweat glands:*

1. Through stimulation of the sweat center, direct or reflex.
2. Through peripheral stimulation of the nerve endings or gland cells.

There is some difference in the **character of the sweat,** according to whether it is obtained by *A* or *B*.

Sweat A. The sweat which results *from increased circulation* is poorer in solid substance and is more alkaline. It has more the general character of a serous exudate. The skin is warm and red.

Sweat B. That obtained by *direct action on the gland* is more concentrated and less alkaline. The skin is pale and cold.

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[1] This is generally the effect of drugs which stimulate the vasomotor center.

This latter is the "*cold sweat*" which is ordinarily produced by stimulation of the sweating center through CO_2, and which is rightly considered a serious omen in the course of a disease, since it indicates asphyxia.

Children sweat more, old people less easily, than adults. Amongst animals, horses sweat most profusely; pigs and beef, not very readily; dogs, rabbits, and sheep not at all; cats only on the paws.

ENUMERATION OF DIAPHORETIC MEASURES.

The diaphoretics may be divided, according to the manner of their action, into the following classes:

1. Application of External Heat.— This may be by *hot air, vapor, water, or sand-baths.*

The latter, which unfortunately can only be carried on in special institutions, consists in burying the patient up to the shoulders in hot sand; it has the advantage over the others in rapidly absorbing the fluid and thus preventing maceration of the skin.

2. The heat may be increased by **preventing the loss of the body heat,** either by protection from the external temperature or by preventing evaporation (through gutta percha, etc.). *Packing* may be counted here.

3. Artificial heat may also be supplied *internally* through *hot drinks.*

This will also *increase the quantity of urine,* and will therefore not be resorted to when the securing of rest to the kidneys is the main object intended, nor when it is desired to diminish the amount of fluid in the body. But it is an excellent method for indications 2, 3, and 4. (See below.) *Hot water* alone will accomplish the result, but it is usual to give it in the form of *infusion* of aromatic herbs, which tend to make it less nauseating and possibly aid the sudorific action. Amongst these may be mentioned elder and linden flowers, chamomile, anise, elm, sage (teacup or two of infusion, 1 : 15, ounce to pint).

4. Dilators of Cutaneous Vessels.— Amongst these, *alcohol* (in the form of hot punch) holds the first place. Then come the nitrites, especially *Spiritus Ætheris Nitrosi* (2 c.c. ʒss).

Atropin and morphin also have this effect, but the former suppresses sweat on account of the paralysis of the nerve endings.

Morphin forms an ingredient of the diaphoretic *Dover's powder.*

A dilatation of the skin vessels may also be produced by **irritation of the cutaneous nerves,** either from the circulation (*aconite,* ½ drop of tincture) or locally by counter-irritants (*sinapism,* see Chap. XXIX.).

5. Nauseants.— Diaphoresis forms one of the features of the nausea stage of emetics, and any one of the latter may be employed for this purpose, if its action can be easily restricted to the desired limit. *Dover's powder* (5 grs.) is the one most used, as it also has the dilator and general narcotic action of the morphin.

6. Stimulation of the sweating center may be obtained by *camphor,* but *ammonia* (especially in the form of *Liq. Ammon. Acet.* ʒss to j) is the most useful.

7. Stimulation of the Peripheral Secretory Nerves.—To this class belongs the whole pilocarpin series, of which, however, as we have pointed out, the *pilocarpin* itself is alone used in practice.

INDICATIONS FOR DIAPHORETICS.

These were at one time innumerable; they were then almost entirely neglected, and have been re-introduced to any great extent only comparatively recently. They may be *summarized* as follows:

1. Removal of liquid from the body.
2. Removal of poisons.
3. To re-establish a disturbed circulation.
4. Relief of kidneys.
5. To increase alkalinity of tissues.
6. In ophthalmology.
7. To reduce temperature.

1. Removal of Liquid from the Body:

(a) to cause the *absorption of exsudates.*

(*b*) in *obesity,* withholding carbohydrates at the same time, to oblige the body to form the water which it requires, by the combustion of its adipose tissue.

For these purposes any of the diaphoretic measures, with the exception of hot liquids, may be used, either singly or in combination.

2. Removal of poisons introduced from without or formed in the body: this is especially valuable in chronic intoxications, as by As, Pb, Hg; nicotin, morphin, bacterial poisons (in fevers, etc.); snake and spider bite; uremia, gout, myxedema, etc.

3. To re-establish disturbed circulation in the skin, and thereby to *relieve congestion* of internal organs: this determines their use in colds, rheumatism, etc.; in cold skin from whatever cause; in inflammation of lungs, pleura, etc. When a strictly local congestion is to be relieved, the same results may be obtained by counterirritants (see Chap. XXIX.).

The increased vascularity of the skin is also used to hasten the outbreak of *febrile exanthemata, to promote the absorption of salves, etc.* Further, in certain *diseases of the skin* where its nutrition is defective.

4. To Relieve Inflamed and Overtaxed Kidneys.— The amount of excrementitious material removed by a thorough sweating is really quite large, and this gives the kidneys a good measure of functional rest.

Ordinary sweat (Hoelscher, 1904) contains 0.22 to 0.81% of ash, and 0.043 to 0.084% of nitrogen, mainly in the form of urea. The sweat excreted under the influence of pilocarpin contains in normal individuals 0.051 to 0.085% of nitrogen, and 0.26 to 0.31% of ash. Three liters of sweat — a not unusual quantity after pilocarpin — would therefor remove about 2.5 Gm. of nitrogen. In nephritis, the nitrogen content may be much higher, to 0.288%; so that the three liters could remove to 8 Gm. of nitrogen. This indicates how efficiently the kidneys may be relieved by diaphoresis. This is also shown by the examination of the blood: the abnormally great depression of the freezing point of the blood of uremic patients may be reduced to normal by diaphoresis (Bendix, 1904). The freezing point of the blood of normal animals is not affected. Alimentary glycosuria could also be prevented by free diuresis, the excess of sugar being excreted by the skin.

5. To increase the alkalinity of the tissues, in gout, oxybutyric acid coma (diabetes), etc. Drugs which stimulate the glandular activity directly, such as *pilocarpin,* must be employed here, since the sweat is acid only when produced in this manner. This removal of acid is so marked that the urine of healthy individuals may be made markedly alkaline by an injection of pilocarpin. The acidity of the gastric juice may also be diminished.

6. In **Ophthalmology,** diaphoresis has been found useful in congestive and exudative lesions of the uveal tract, in retinal detachment and in toxic blindness; it is useless in atrophic and cicatricial lesions.

7. The **Reduction of Temperature** is considered in Chapter XVII.

(N) MATERIA MEDICA.

(**Muscarin*, not used; dose would be 10 to 100 mg.)

Pilocarpus (U. S. P.) [**Jaborandi Folia,** B. P.].—*Jaborandi.*—Leaflets of *Pilocarpus microphyllus* and *P. Jaborandi,* Rutaceæ. Brazil.

Pilocarpin (¼ to ½%), Pilocarpidin, isopilocarpin; (at least 0.5% of total alkaloids, U. S. P.); Gums; Volatile Oil.

P. Jaborandi is scarcely to be found in commerce.

Fluidextractum Pilocarpi (U. S. P.) [Extr. Jaborandi Liquidum, B. P.].—One-half alcohol; 0.4% of alkaloid (U. S. P.) [Alcohol, B. P.]. Turbid with water. *Dose:* 0.3 to 2 c. c. (5 to 30 minims) (2 c. c. = 30 ♏., U. S. P.).

Tinctura Jaborandi (B. P.).—20%. One-half alcohol. *Dose:* 2 to 4 c. c. (30 to 60 minims).

Pilocarpinæ Hydrochloridum (U. S. P.).—$C_{11}H_{16}N_2O_2.HCl$. Sol. 0.3 water, 2.3 alc. *Dose:* 5 to 10 mg. (1/12 to ⅙ gr.) (10 mg. = ⅕ gr., U. S. P.); usually hypodermically. Locally in eye, 2%.

Pilocarpinæ Nitras (U. S. P., B. P.).—$Pil.HNO_3$. Sol. 4. water; 60. alc. *Dose:* as the preceding.

* **Curara.**—The important constituents have already been noted. The different samples of the drug vary so widely that no dose can be set down. Of an average active sample 0.008 to 0.04 Gm.—of curarin, 0.0025 to 0.03 Gm.—intravenously, have been stated to be efficient in man.

* **Tabacum.**—The dried commercial leaves of *Nicotiana Tabacum,* Solanaceæ; cultivated. Obsolete. The dose is given as 0.5 Gm.

Nicotin, $C_{10}H_{14}N_2$, is a fluid, volatile, oxygen-free alkaloid, of strongly basic characters. It forms salts, most of which are soluble. It is colorless and almost odorless when freshly prepared; but it partly decomposes on keeping, acquiring a characteristic odor and a brown color. The dose would be to 0.001 Gm.

Conium (U. S. P.) [**Conii Fructus,** B. P.].—(*Spotted Hemlock.*) Fruit of *Conium Maculatum,* Umbelliferæ. Europe and Asia; naturalized in North America.

Conii Folia, B. P.

The principal constituents have been given (page 268). (At least 0.5% coniin, U. S. P.)

The *preparations* are not reliable.

Fluidextractum Conii (U. S. P.).—Acidulated dilute alcohol; 0.45% coniin. *Dose:* 0.06 to 0.3 c. c. (1 to 5 minims) (0.2 c. c. = 3 ♏., U. S. P.).

Succus Conii (B. P.).—3% of the juice. *Dose:* 4 to 8 c. c. (1 to 2 drachms).

Unguentum Conii (B. P.).—From the juice.

Tinctura Conii (B. P.).—20% in three-fourths alcohol. *Dose:* 2 to 4 c. c. (30 to 60 minims).

**Coniin,* $C_8H_{17}N$.—Dose: 0.002 to 0.005 Gm.

Gelsemium (U. S. P.) [**Gelsemii Radix,** B. P.].—(*Yellow Jasmine.*) Rhizome and roots of *Gelsemium sempervirens,* Loganiaceæ. Southern United States.

* Gelsemin and Gelseminin; Volatile Oil; Resin.

Fluidextractum Gelsemii (U. S. P.).—Alcohol. *Dose:* 0.05 c. c. = 1 ♏.

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* Not official.

Study Materia Medica Lesson 23.

Tinctura Gelsemii (U. S. P., B. P.).—10%; ⅔ alcohol. *Dose:* 0.5 c. c. = 8 ♏.

* *Gelseminin*, $C_{22}H_{26}N_2O_3$.—*Dose:* 0.0005 to 0.002.

Lobelia (U. S. P., B. P.).—(*Indian Tobacco.*) Leaves and tops of *Lobelia inflata* (collected after a portion of the capsules has become inflated), Lobeliaceæ. North America.

Lobelin ($C_{18}H_{23}NO$).

Fluidextractum Lobeliæ (U. S. P.).—Diluted acetic acid. *Dose:* 0.05 to 0.5 c. c. (1 to 10 minims).

Tinctura Lobeliæ (U. S. P.).—10%. One-half alcohol. *Dose:* Expectorant, 1 c. c. = 15♏.; emetic, 4 c. c. = 1ʒ.

Tinctura Lobeliæ Ætherea (B. P.)—20% in spirit of ether. *Dose:* 0.3 to 2 c. c. (5 to 30 minims).

Scoparius (U. S. P.) [**Scoparii Cacumina,** B. P.].—(*Broom Top.*) The tops of *Cytisus Scoparius,* Leguminosæ. Western Asia and Southern Europe; naturalized. *Dose:* 1 Gm. = 15 grs.

Spartein, Scoparin, Tannic Acid.

Sparteinæ Sulphas (U. S. P.).—$C_{15}H_{26}N_2.H_2SO_4 + 5H_2O$. Sol. 1.1 water, 2.4 alc. *Dose:* 0.006 to 0.03 Gm. (1/10 to ½ grs.) (10 mg. = ⅕ gr., U. S. P.).

Infusum Scoparii (B. P.).—10%. *Dose:* 30 to 60 c. c. (1 to 2 ozs.).

Succus Scoparii (B. P.).—3% of the juice. *Dose:* 4 to 8 c. c. (1 to 2 drachms).

Physostigma (U. S. P.) [**Physostigmatis Semina,** B. P.].—(*Calabar Bean.*) The seed of *Physostigma Venenosum,* Leguminosæ. Tropical Western Africa. *Dose:* 0.1 Gm. = 1½ grs.

Physostigmin, Eseridin, Calabarin. (At least 0.15% alkaloids, U. S. P.)

Eseridin has an action similar to Physostigmin, but weaker. Calabarin belongs to the Strychnin group.

The liquid preparations spoil very rapidly and are unreliable unless freshly made.

Hallauer (1899) claims that the reddening does not interfere with the miotic action, but renders the solutions more irritant.

Extractum Physostigmatis (U. S. P., B. P.).—Alcohol. Powdered; 2% alkaloids. *Dose:* 0.006 to 0.015 Gm. (1/10 to ¼ grain) (8 mg. = ⅛ gr., U. S. P.).

Tinctura Physostigmatis (U. S. P.).—3% Alcohol, 0.014% alkaloids. *Dose:* 0.6 to 2 c. c. (10 to 30 minims) (1 c. c. = 15 ♏., U. S. P.).

Physostigminæ (Eserinæ) *Sulphas* (U. S. P., B. P.).—$(C_{15}H_{21}N_3O_2)_2.H_2SO_4$. Very sol. in water or alc. *Dose:* 0.5 to 2 mg. (1/100 to 1/30 gr.) (1 mg. = 1/64 gr., U. S. P.). Locally in eye, 1/10 to ½%.

Physostigminæ Salicylas (U. S. P.).—Sol. 72.5 water, 12.7 alcohol. *Dose:* as the preceding.

Lamellæ Physostigminæ (B. P.).—Each, 1/1000 grain.

CHAPTER XIII.

INTERNAL SECRETIONS.

Internal secretions may be defined as specific substances formed within a glandular organ and given off to the blood or lymph. (Howell.)

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* Not official.

This subject is generally treated in text-books of physiology; but it belongs equally to pharmacology, since the actions of these substances are strictly pharmacologic; and their importance in therapeutics is second only to their physiologic significance.

Historical.— The phenomena of life are often associated with the production of poisons. A great variety of these poisons is elaborated by plants and by lower animals; and they serve important functions in the economy of these organisms. It would seem logical to look for similar active substances in the higher forms of life. Such were found to some extent in the ordinary excretions, but the discovery of active internal secretions is of comparatively recent date.

Our knowledge of this subject was started by Claude Bernard's discovery of the glycogenic function of the liver. Brown-Séquard, basing himself upon this mainly, advanced the brilliant theory of what he was the first to call "internal secretion," of its important functions to the organism, and suggested it as a possible new field in therapeutics. Séquard demonstrated none of these secretions, much less their passage into blood and lymph. Since that time great advance has been made along this line. Internal secretions have been demonstrated in glands with and without ducts. Fatal effects of excision of some of these organs — *e. g.*, the thyroid — first served to direct attention to their secretory function. Further investigations showed that the extracts of these glands possessed specific physiologic properties. The latter correspond for the most part to those of members of the series comprised in this treatise between the extremes of atropin and physostigmin.

A powerful impulse was given to this field of investigation, and it was soon found that most tissues — nervous and muscular, as well as glandular — produce some effects (especially on blood-pressure), when the extracts are injected into the circulation.

These discoveries found immediate practical application in pathology and therapeutics — often without awaiting the thorough scientific investigation of the substances. These empiric uses and speculations are open to severe criticism. But the important results which have followed the scientific study of the suprarenal and thyroid secretions, etc., are sufficient to show that the field has great possibilities, approaching in importance the antitoxins and ferments, which are in a sense internal secretions.

The investigation of these substances must bear on the isolation and chemic study of the active substance, its actions, its functions in physiology, and its effects in disease.

It is very probable that the chemic characters differ for the various principles. The active principle of suprarenal is an alkaloid; that of thyroid is a constituent of a proteid (but is not itself a proteid); the others have not been isolated sufficiently pure for identification.

Manner of Action.— There has been considerable discussion as to whether the function of these substances is antitoxic or physiologic — *i. e.*, whether they are chemically or functionally active.

They certainly are the latter, for their physiologic activity is easily demonstrated by injection or feeding. As to the former — the chemic destruction of poisons by them — very little is known. However, some of them favor oxidation, which is undoubtedly a normal aid in the removal of poisons. Such chemic and oxidative action is also rendered very probable by the fact that blood of animals from whom the glands have been excised is toxic to other animals, especially when the glands from these have also been removed. But even this is not decisive, for it still remains to be shown whether it is the gland itself or its products which possesses the antitoxic action.

These glands appear to vary considerably in their activity at different ages. Thus, the thyroids are more active in children, almost inactive in old people. The activity of the glands appear comparatively early in the embryonic life, the order varying somewhat in different genera: In the human embryo, first in the thymus, then the thyroid, and lastly the suprarenal. At birth, the thyroid is devoid of iodin.

The bad effects following the excision of these glands can n all cases be removed if the gland substance is administered. This is usually active when given by the mouth, which constitutes a very marked difference from antitoxins. The latter are typical proteid bodies (globulins), and are destroyed in the stomach.

I. SUPRARENAL ALKALOID.

Active Principles.— The active principle of the suprarenal glands is a typical alkaloid which has been named *epinephrin,* suprarenin, adrenalin, etc. Its *formula* is given by Abel as $C_{10}H_{13}NO_3-\frac{1}{2}H_2O$ (the H_2O being water of constitution, not of crystallization).[1] Epinephrin can also be obtained in an amorphous non-hydrated form. Derivatives have been obtained from both forms, some of these being active, others inactive. The hydrate is precipitated in somewhat impure form as crystals, when ammonia is added to a concentrated solution. This reaction is the basis of the *preparation* of the commercial crystalline alkaloids (first prepared by Takamine). It is fair to state that other investigators claim a slightly different composition. The moist gland contains at least 0.3% of the alkaloid, which is found exclusively in the medulla; it is often absent in glands which have undergone pathologic changes. (The gland in man would contain about 7 mg.).

Fate in Body.— The alkaloid seems to be very slowly *absorbed* from hypodermic injection, and scarcely at all from the stomach. On the other hand, it is very rapidly *destroyed* in the body by oxidation. For these and other reasons, the action is very short, and very little effect is obtained by hypodermic or gastric administration. Little, if any, is *excreted* as such in the urine. The solutions are not affected on boiling for a short time, but alkaline or neutral solutions are oxidized on exposure to the air; dilute solutions do not keep well.

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[1] The formula of adrenalin is given as $C_9H_{13}NO_3$ (Aldrich).

SUMMARY OF ACTIONS.

Epinephrin stimulates the physiologic endings of sympathetic nerves, in smooth muscle and in glands. (In structures in which sympathetic stimulation lowers the tone, epinephrin also causes relaxation.) It also has a stimulant action on cardiac and striped muscle.

It has but little effect on the central nervous system. The actions are only obtained typically on local or intravenous administration. They disappear quickly. The stimulations are not followed by paralyses.

The actions of epinephrin result in the following phenomena:

1. *Rise of blood-pressure,* due to vasoconstriction, mainly of the systemic arterioles (stimulation of constrictor endings).

2. *Slowing of the heart,* due to vagus stimulation, mainly secondary to the high blood-pressure.

3. *Increased contractility of the cardiac muscle* (digitalis action).

4. *Contraction or relaxation of unstriped muscle* in many situations (stimulation of sympathetic endings). The effects are somewhat variable for different animals.

In some situations the unstriped muscle is not affected. The situations in which the muscle is *excited* to contraction are: Arterioles, dilator of iris (*mydriasis*), uterus, seminal vesicles and vas deferens (anal sphincter in some animals), erectores pilorum. The muscles which are *depressed* and relaxed by epinephrin are: Stomach, intestine (*lessened peristalsis*), biliary and urinary bladder (anal sphincter in some animals).

5. Prolongation of the contraction of striped muscle (*Veratrin action*).

6. *Stimulation of secretory cells* in the salivary glands, bronchial mucosa, lachrymal glands, and increased secretion of bile (the effect on sweat is uncertain). The effect, like that on unstriped muscle, occurs after the degeneration of the postganglionic fibers.

7. *Depression of the respiratory center* on intravenous injection, but increase of respiration on subcutaneous administration.

8. *Glycosuria,* due to the conversion of glycogen into sugar.

9. Epinephrin has *no effect on nerve trunks, nor on sensory nerves.*

Details of Important Actions — Circulation.[1]— The intravenous injection of epinephrin in a normal animal produces the striking phenomena depicted in Fig. 62, first described by Oliver and Schaefer, 1894. The blood pressure rises sharply; as it approaches its maximum, the heart-beats are greatly slowed and strengthened. The pressure is not sustained, but returns quickly to normal. The heart-beats also return to their former rate; but, as may be seen from the tracing, more slowly than the pressure.

These phenomena are due to the interaction of three factors: vasoconstriction, vagus-stimulation, and stimulation of the cardiac muscle.

Stimulation of the Cardiac Muscle.— The perfusion of adrenalin through the excised mammalian heart (Hedbom, Cleghorn, Gottlieb, Boruttau), or its direct application to a frog's heart, quickens the rate, and increases the amplitude of the contraction (Fig. 63). The tone is very markedly increased, often doubled. These actions occur after atropin. Existing irregularities are removed, and the effects of muscular depressants are counteracted. A heart which has ceased to beat may often be revived by this drug (Fig. 64). The action is therefor entirely analogous to that of digitalis. (Indeed, the whole effect of suprarenal on the circulation bears a close resemblance to that of digitalis, at least superficially.) The cardiac stimulation plays a subordinate part in the rise of blood-pressure.

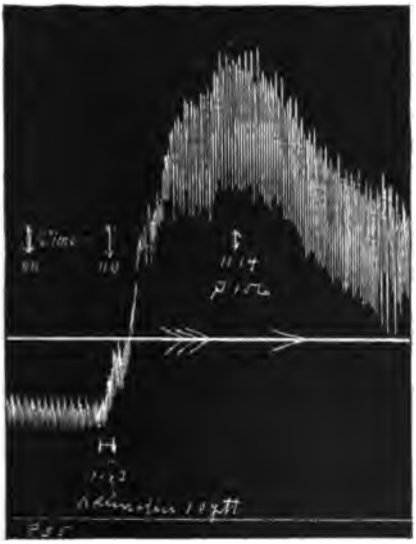

Fig. 62.— Suprarenal on Blood-pressure, dog. 1½ drops per Kg. of 1.1000 adrenalin injected intravenously at H. P.= Blood-pressure in m. m. of Hg.

It cannot yet be definitely stated whether the stimulation involves the muscle-fibers or the accelerator endings.

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[1] Exercise 59.

Vagus Stimulation.— In intact animals, suprarenal slows the beat very materially (in contrast to its effect on the excised heart), the excursions being increased proportionally to the slowing. The phenomenon corresponds to vagus stimulation, and is indeed absent if the vagi have been cut. The vagus excitation is therefor central. As may be seen on the tracing, the slowing occurs only *after* the rise of blood-pressure. This suggests that it may be an indirect effect, *i. e.*, that the vagus center may be stimulated by the rise of blood-pressure, rather than by the suprarenal. This conclusion is confirmed by the observation that the slowing disappears at once if the blood-pressure is reduced to the normal, by bleeding; it is also absent when adrenalin is injected after the vasomotor endings have been paralyzed, but when the vagus endings are quite active. Some observers, however, claim that the vagus is also stimulated peripherally.

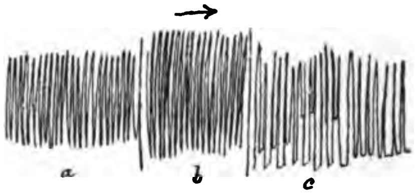

Fig. 63.— Suprarenal extract on isolated heart (after Hedbom): *a*, Normal; *b*, four minutes after injection; *c*, five to six minutes (Langendorff method.)

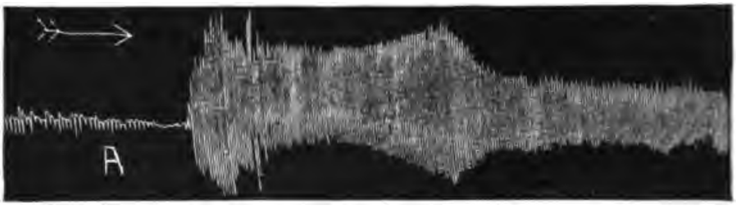

Fig. 64.— Revival of Langendorff heart by adrenalin. The drug is added at A.

The slowing tends to lessen the rise of blood-pressure, and this mounts much higher if the vagi are cut.

A *secondary increase of the pulse-rate* is sometimes seen, and is attributed to central and peripheral stimulation of the accelerator nerves (Neujean, 1905).

The Vaso-Constriction.— It can be easily shown that this is the main cause of the rise of blood-pressure, for the volume of organs, the venous pressure, and the outflow of blood from veins are all diminished during the rise of the arterial pressure. The vaso-constrictor stimulation is mainly *peripheral*, for it occurs equally readily if the central nervous system has been destroyed; furthermore, the addition of suprarenal to the fluid stops the flow through excised organs almost completely (Bier, 1897). The constriction can also be produced locally, by the direct application of suprarenal solutions to mucous membranes or open surfaces. A stimulation of the vasomotor center, if it occurs at all, must play a very subsidiary rôle to this peripheral stimulation.

The rise of pressure is, within certain limits, roughly proportional to the dose of the suprarenal. Even very large doses (7,000 times the effective quantity) do not paralyze the vasomotor mechanisms.

Differences in the Susceptibility of Special Vessels.— Whilst the bulk of the vessels in the body respond to suprarenal by constriction, the effect is not uniform on all. The strongest constriction is observed in the splanchnic and muscular vessels. The effect is less on the vessels of the skin; it is weak or absent in the cerebral and pulmonary vessels. (Brodie and Dixon, 1904, failed to find any constriction in the latter, but Plumier, 1904, claims that it occurs, although weakly and only with large doses.) The kidney vessels, in the intact body, are first strongly constricted, diminishing the urine flow; but they dilate when large doses are used, increasing the urine (Bardier and Frenkel, 1899).

Those vessels which are but little affected by the direct action of the suprarenal, *f. i.,* the cerebral vessels (Neujean, 1905), are passively dilated in the intact animal, on account of the displacement of the blood from the more powerfully constricted areas.

Dilator Action of Suprarenal.— Brodie and Dixon often observed that the vessels were dilated by suprarenal. In the freshly excised kidney, suprarenal causes a powerful constriction; but some time after the excision, it dilates the vessels (Sollmann, 1905). The same phenomenon was observed in the post-mortem perfusion of the dog's leg. In the ear of the living rabbit, the constriction is also followed by dilation (Meltzer and Auer, 1904).

It is evident that suprarenal stimulates a dilator, as well as a constrictor mechanism. The constrictor action is so much more powerful, that the dilation can only be seen in organs which do not respond by constriction, naturally or through injury to the constrictor mechanism; the dilator mechanism being evidently less affected by injury.

Structures Affected by Suprarenal.— The peripheral action of suprarenal could be exerted either on the nerve endings or on the muscle or gland cells. (Ganglia can be readily excluded.) If the action were directly on the cells, one would expect the effects on different structures to be rather uniform. This is not the case; and it is rather suggestive that the effect on all organs whether it increases or inhibits their function, correspond quantitatively and qualitatively with the effects of stimulation of *sympathetic* nerves;[1] whilst cells not supplied with sympathetic innervation (such as the muscles of the bronchioles), do not respond to suprarenal. Brodie and Dixon have further shown that the (vascular) effects are prevented by apocodein, which paralyzes the sympathetic endings; whilst barium (which acts directly on the muscle) is not hindered by apocodein. Chrysotoxin (ergot) acts in the same manner as apocodein (Dale — Sollmann and Brown, 1905). Only one conclusion seems admissible, viz., that *suprarenal acts by stimulating the sympathetic endings.* It has been found, however, that it preserves its action for several weeks after section of the sympathetic nerve, peripheral to the ganglia (Elliott, Hamburger), when the nerve fibers have presumably degenerated. This can be explained on the assumption that the physiologic nerve endings, which are stimulated by suprarenal, do not degenerate on section of the nerve.

The Cause of the Brief Action of Suprarenal.— The action of suprarenal disappears within a few minutes, as may be seen from Fig. 62. The instability of suprarenal in alkaline solution seemed to explain this brief action; direct experiments, however, have shown that this explanation does not suffice. Emden and von Fuerth (1903) found that the activity is but little impaired, in this short time, by digesting adrenalin with blood and organs. They suggested that the disappearance of the action might be due to diffusion into the tissues. Weiss and Harris (1904), however, showed that the adrenalin is still present in the blood, at a time when its action has completely disappeared; for they found that when the blood was withdrawn at this time and injected into a second animal, the latter showed the typical adrenalin rise. Ehrmann (1905) has confirmed this, using the mydriatic effect on the frog's eye as indicator. (DeVos and Kochmann (1905) claim, however, that it disappears within 3 to 10 minutes.) Nor can we account for the fugitive effect by assuming that the vessels cease to respond: for a renewed injection of adrenalin, made at this time, will again raise the pressure; and continuous injection of adrenalin, or continuous perfusion of excised organs, will exhibit the action for a long time. A sufficient explanation of the quick recovery of blood pressure is therefore wanting. Destruction of the epinephrin is undoubtedly a contributing factor, and is perhaps principally involved in the inactivity of suprarenal when administered hypodermically.

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[1] First pointed out by Langley, 1901, and extended by Elliott, 1904 and 1905.

The **suprarenal glycosuria**[1] has been studied especially by Herter and Wakeman (1902) and by D. Noël Paton (1903). The kidneys are not involved in the produotion of this glycosuria. The excretion of sugar is markedly higher on carbohydrate diet, or in animals rich in glycogen; but some sugar is excreted even by glycogen-free animals on a non-carbohydrate diet; the sugar may therefor come in part from proteids, just as in pancreatic diabetes; indeed, pancreatic and suprarenal glycosuria present many analogies. In either case, the process consists mainly in a lessened utilization of sugar. The excretion of urea, and especially of ammonia, is markedly increased in suprarenal diabetes, especially if carbohydrates are deficient. The urine does not contain acetone nor diacetic acid. The glycosuria can be produced by hypodermic as well as by intravenous injection. It is especially marked when suprarenal solution is painted on the pancreas, but it is quite possible that this glycosuria involves another mechanism (stimulation of afferent nerves). Other reducing substances also produce this glycosuria when applied to the pancreas. Underhill (1905) showed that piperidin, nicotin, etc., also cause glycosuria when painted on the spleen, or when injected into the circulation or peritoneum. The effect is therefore not due to a direct action on the pancreatic cells, but may be circulatory.

Influence of Dosage on the General Effects.— The effects of intravenous injection vary with the dose. The results of increasing doses may be tabulated as follows (Langley, 1901):

(*a*) Rise of blood pressure.

(*b*) Inhibition of bladder, mydriasis.[2]

(*c*) Contraction of uterus, vas deferens, and seminal vesicles; salivation and lachrymation; inhibition of stomach and gall-bladder; increased bile secretion; inhibition or stimulation of internal anal sphincter.

(*d*) Contraction of erectores pilorum.

(*e*) Uncertain effect on tunica dartos and on sweat.

Toxic doses cause vomiting, excitement, debility, bloody diarrhea, hematuria, ascending central paralysis, great fall of temperature, occasionally convulsions, complete prostration, and *death* by respiratory (cat) or cardiac (dog) paralysis. The *fatal dose* (0.1 to 0.2 mg. per Kg. intravenously, or 5 to 6 mg. per Kg. hypodermically) is about

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[1] Exercise 34.

[2] The influence of the cervical sympathetic ganglion on the pupillary effects of adrenalin are described by Meltzer & Auer (1904).

500 times the therapeutic dose. A noticeable rise of blood-pressure can be seen after $^1/_{1000}$ of the fatal dose.

Small hypodermic doses increase respiration, pulse-rate, metabolism, and temperature, without altering the blood pressure.

Suprarenal Atheroma.— This was first produced by Josué (1903) by repeated intravenous injection into rabbits. The essential lesion consists of degeneration and calcification of the elastic fibers of the tunica media of the larger arteries, beginning in the aorta. This results in parietal aneurisms, extending to the hilus of organs. (The lesions do not correspond with those of arterio-sclerosis.) Erb (1905) concludes that the atheroma is caused by a direct toxic action, and not by high blood pressure; for it occurs with intraperitoneal injections, which do not affect the pressure.

No tolerance is induced.

Excision of both suprarenal glands produces death in a few days. There is fall of blood-pressure, muscular weakness, decrease of metabolism, fall of temperature, central paralysis, death by failure of respiration.

The injection of the blood of the moribund animals into a normal specimen causes analogous symptoms. Unilateral excision has usually little effect.

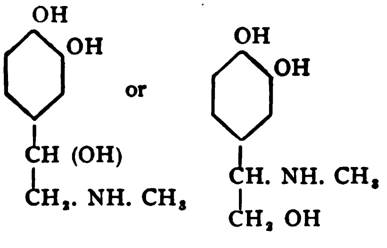
That the active substance is actually excreted by the glands into the blood is shown by the fact that the blood of the suprarenal vein produces the typical effect. The substance is carried in the plasma, not the corpuscles.

Elliott (1905) believes that adrenalin is also present in special cells in other situations, but always closely associated with sympathetic ganglia (*f. i.*, in the intercarotid body). This indicates that sympathetic stimulation is affected by both a chemic and a nervous mechanism.

Relation to Other Groups.— Epinephrin is related chemically to *piperidin* and *pyrocatechin*. These produce a similar rise of blood pressure, but they also stimulate the respiratory center. The action on muscles and endings places epinephrin in the *pilocarpin group;* its action on the heart is related to that of *digitalis,* that on skeletal muscles to *veratrin.*

It is stated that epinephrin is *antidotal* to toxic doses of nicotin, atropin, neurin, and strophanthin, so that some of the resemblances seem to be rather superficial.

Synthetic Epinephrins.— A number of related structural formulæ have been proposed for suprarenal alkaloid. The two following are the most commonly accepted:



According to these, the alkaloid consists of a catechol nucleus with an oxyethyl methyl amin side-chain. Very similar products can be prepared synthetically, and a number of these act very similarly to suprarenal. Loewi and H. Meyer (1905) found that amino-acetyl-catechol, and its methyl and ethyl derivatives produced the typical effects of adrenalin on the arterioles, heart, and pupil, as also the glycosuria and atheroma; larger doses, however, were required. Dakin (1905) has prepared a synthetic base which approaches adrenalin still closer in its composition, and which corresponds to it quantitatively in its actions. The activity appears to reside in the catechol nucleus, but to be greatly enhanced by the introduction of the above or similar side-chains.

THERAPEUTIC USES.

The **vasocontrictor action** of the suprarenal preparations is the most important of these actions from the therapeutic standpoint. They surpass all other drugs in this respect. The *local application* is most effective. The 1 : 10,000 to 1 : 1,000 solution of the alkaloid is used *to check capillary hemorrhage* in situations accessible to its local application (especially in nasal and laryngeal operations); as also against gastric hemorrhage. *Chewing of suprarenal tablets* arrests nasal, pulmonary and gastric hemorrhage, probably by a reflex vasoconstriction. The preparations in the above strength are often employed in conjunction with *cocain* to prevent the absorption of this alkaloid, thereby increasing its local action and lessening its systemic effects. Suppositories are used against bleeding hemorrhoids.

Beneficial effects from suprarenal are also claimed in *hay-fever*. The treatment consists in local application to the mucous membrane of the nose, and chewing the tablets, once or twice a day, beginning two or three weeks before the expected attack and continuing throughout the season.

The powerful *general vasoconstriction* which can be secured by the suprarenal preparations would render them very useful in vasomotor depression, especially in *shock* and in the *accidents of anesthesia*.[1] Their usefulness is, however, limited by the difficulty of their administration. No effect can be expected from their use by mouth, and even hypodermic injection (combined with massage of the site of injection) is uncertain and not sufficiently powerful. Clinically, however, it has been observed that the hypodermic injection of small doses of adrenalin seems to cut short paroxysms of asthma, without being either curative or prophylactic. Intramuscular injection is more effective (Meltzer and Auer, 1905). To secure a marked and lasting rise, the drug must be used intravenously, and almost continuously. Extracts are inadmissible, on account of the danger of sepsis. A 1 : 10,000 solution of the alkaloid should be injected drop by drop into a superficial vein, until the desired result is obtained. This method promises good results, but has not yet been tried sufficiently to judge its value.

The *cardiac action* of suprarenal has little value, for equivalent effects can be secured more easily, and with less vaso-constriction, by means of digitalis.

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[1] Exercise 58.

Suprarenal preparations have also been recommended in *Addison's disease,* rickets, diabetes insipidus, etc. The results have not been very good, which is scarcely surprising when the rapid destruction of the substance is considered.

Adrenalin has been suggested as an antidote to *acute morphin poisoning,* on the theory that the latter diminishes the suprarenal secretion. The results on animals have been favorable (which does not commit us to the theory that morphin influences the suprarenals). It has not been tried on the human subject (Reichert, 1901).

MATERIA MEDICA.

Glandulæ Suprarenales Siccæ (U. S. P.).—The dried and powdered glands of the sheep or ox. One part = 6 of fresh glands. *Dose:* 0.25 Gm. (4 grs.). A fairly permanent solution can be made by dissolving 15% of the powder in 2% carbolic acid and filtering. Also in the form of *Tablets: Dose:* 1 to 3.

* *Epinephrin* (found on the market under the name of adrenalin, suprarenalin, etc., in crystals or in 1 : 1,000 solution in normal saline, preserved with some antiseptic). The *hydrochlorid* is the salt commonly used. *Administration:* see under therapeutics; locally as 1 : 10,000 to 1 : 1,000 solution, internally 5 to 30 drops of 1 : 1,000. *Incompatibilities* as for alkaloids.

The alkaloid gives a very characteristic reaction with *ferric chlorid,* an emerald green color, which turns purple and carmin on adding an alkali.

II. THYROID.

The effects of the thyroid glands need to be studied from two aspects: The effects resulting from a deficient secretion; and those produced by the presence of an excessive amount of secretion. The former will be considered first, as being the most conspicuous.

1. EFFECTS OF THYROIDECTOMY.

The total removal of the thyroid gland is fatal to most animals (as was shown by Schiff in 1856); but the symptoms differ considerably in different species, in violence and in the rapidity of their development; they are also more violent in young individuals than in old age. Two forms of effects may be distinguished: the acute (seen in dogs) and the slow form (seen in man and in the monkey).

The *slow form* is identical with the disease known as *myxedema,* cretinism, etc. A dulling of the mental faculties accompanies ill-understood changes of metabolism. The latter lead to general cachexia, and to myxedema, a hyperplasia of the subcutaneous connective tissue, which reverts to the mucous embryonal type. The mental and physical development of children is greatly stunted. (The myxedema is absent in those animals which die acutely, within a few days.)

These symptoms persist for a variable time, terminating finally in those of the acute form.

In the *acute form* the metabolic changes are also a prominent feature, being indicated by cachexia, by disturbed heat-regulation, and by a loss of red blood corpuscles. In addition, however, there are very conspicuous nervous disturbances; the motor system shows an increased reflex excitability, increasing to choreic spasms (tetany), and to intermittent convulsions. The seat of these is central, but not in the motor areas. Diminished cutaneous sensibility is also present. The animals die in a few days, without well-defined lesions.

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* Not official.

Study Materia Medica Lesson 23.

A certain proportion of dogs do not show much change after thyroidectomy. It is found in all these cases that the animal possesses *accessory thyroids.* These may be situated in various places, often in the neck or near the arch of the aorta, and possess the same structure as the thyroid gland. They hypertrophy after removal of the latter.

Rabbits do not die after removal of the thyroids. However, if certain small glandular bodies lying in the neighborhood of the thyroids — *parathyroids* — are also removed, the animal dies very quickly. In the dog these bodies are situated inside the thyroid gland and are, therefore, removed in the ordinary operation. If they are spared, the dogs also survive more frequently. The removal of these bodies alone in either animal causes death with symptoms similar to those of thyroidectomy. It is possible, however, that their functions are distinct, although similar.

They have also been demonstrated in the sheep, seal, monkey, man, and exist probably in all animals.

2. THYROID FEEDING AFTER THYROIDECTOMY.

The above symptoms may be entirely prevented by leaving a portion of the gland or by transplanting it into any portion of the body, or in man even by feeding with gland substance.

(This thyroid feeding was first tried in 1884.) In dogs and monkeys thyroid feeding is not so uniformly successful, but it saves a certain proportion of these animals also.

The same results follow the administration of the active principle — iodothyrin.

3. THE EFFECT OF INJECTION OF THYROID ON NORMAL ANIMALS.

When thyroid extract is injected intravenously, it increases the tonic impulses and the excitability of the vagus, depressor and dilator nerves, whilst it diminishes those of the accelerators and vasoconstrictors. The blood pressure consequently falls, and the heart is slowed in most animals. In man, however, the heart is commonly quickened, presumably by stimulation of the accelerator center. Thyroid also acts slightly on the cardiac muscle, small doses increasing, and large doses diminishing, the force of the contractions.

It is possible that these circulatory changes are really the basis of the metabolic effects.

4. EFFECTS OF CONTINUED ADMINISTRATION OF SMALLER DOSES.

The effects of the continued administration of smaller doses (such as are seen when overdoses of the substance are taken in the treatment) are somewhat different.

The *symptoms* are partly nervous, partly circulatory. The former consists in insomnia, headache, palpitation, nausea, vertigo, polyphagia or loss of appetite, diarrhea, general malaise, tremors of extremities. The heart's action is irregular and exaggerated, and there are also various vasomotor disturbances.

Effects on Metabolism.— Oxidation is markedly increased, and both nitrogenous and non-nitrogenous bodies are rapidly used up. The temperature rises. However, and in whatever conditions, thyroid is administered, it causes a large increase of N in the urine, but the first effects are upon fat, and it acts upon proteids only when the former have been reduced to a certain minimum. The quantity of urine is also increased. Large doses cause a glycosuria.

Since arsenic retards oxygenation, its use has been suggested to combat this side-effect of the thyroids, and good results have been claimed, but are scarcely sufficiently established.

5. FUNCTIONS OF THE THYROIDS.

The physiologic action of the injection of thyroid extract — the fall of blood pressure and the increase of the irritability of the vagus endings — renders it probable that the gland has an important connection with the *circulation.* Moreover, the gland itself contains powerful vasodilator fibers which can greatly lower the pressure in the carotid, and thereby regulate the cerebral circulation. It is quite conceivable that the nervous phenomena, which follow the injection of extracts or excision of the glands, are in part due to changes in the blood supply of the nervous centers.

It is also possible that the thyroids have some function in *disintoxication.* It is claimed that caffein is more toxic after the excision of the glands, and it is possible that they might act similarly upon poisons generated within the body. Hunt (1905) has found that thyroid feeding lessens the susceptibility to acetonitrile. The serum of thyroidectomized animals is stated to counteract the effects of iodothyrin.

6. ACTIVE PRINCIPLES.

Baumann (1896) succeeded in isolating a principle from thyroid glands, which possess all the physiologic actions, and which he named *iodothyrin.* This substance is especially characterized by a very high content of iodin (to 14.3%, Oswald). It does not give the proteid reactions, and is very resistant to heat and reagents. The investigation of the chemistry of the thyroid was continued especially by Oswald (1899), who showed that iodothyrin does not exist as such in the glands, but is liberated in the process of manufacture from a peculiar globulin (*thyreoglobulin*). This is confined to the colloid secretion of the alveoli. The iodin-content of this globulin varies from 0 to 1.3% or more; usually about 0.35%; the physiologic activity being proportional to the percentage of iodin. An iodin-free thyreoglobulin is also found in thyroids which contain no colloid. Oswald therefor suggests that two globulins occur in the gland, differing only by the presence of iodin, and not separable by reagents. All attempts to increase the iodin of the thyreoglobulin by chemic means, outside of the body, have resulted only in destroying its activity. Within the body, however, it may be somewhat increased by the administration of potassium iodid. It is decreased, on the other hand, by exclusive meat diet. (Meat diet has also been found to hasten death after thyroidectomy, whilst a milk diet prolongs life. This should be remembered in the treatment of myxedema.)

The iodized thyreoglobulin constitutes the main constituent of the healthy colloid secretion of the gland; but this contains also some of the iodin-free globulin, and a small amount of a uncleoproteid, but no mucin. The colloid is secreted into the lumen of the alveoli by the epithelial cells, which may or may not undergo destruction in this process. It is discharged from here into the lymph, usually by rupture of the alveolar walls. The vacuoles existing in the colloid are probably artifacts. Pilocarpin does not increase the colloid secretion.

When iodothyrin is administered by mouth, it appears to be readily *absorbed,* to judge from its prompt action. It is *excreted* by the urine partly unchanged, partly as iodid. The excretion occurs slowly.

Iodin Content of Goitres.— The iodin content of goitres (with the possible exception of exophthalmic goitre) is materially diminished, the thyreoglobulin being poor in this element. (In colloid goitre, for instance, it contains only 0.04 to 0.09%.) This accounts for the symptoms.

The thyroids of the new-born usually do not contain iodin, but this is found in the accessory and para-thyroids. None exists in the thymus. Iodin is also absent from the thyroid glands of calves; these do not contain any colloid.

7. RELATION TO OTHER GROUPS.

The large proportion of *iodin* in iodothyrin might lead to the thought that perhaps the iodin itself had a similar action. This is far from being the case, for the action of the latter or of iodids on intravenous injection is precisely the opposite: The excitability of the vagus fibers is diminished, and the effect of thyroid injection is abolished, while the blood pressure is raised. (Barbèra, 1900).

Sodium phosphate, on the other hand, has the same action on vagus endings as iodothyrin.

These are, therefore, two antagonistic groups: (*a*) Iodothyrin and sodium phosphate increase the excitability of the vagus and depressor endings and cause a fall of blood pressure. (*b*) Iodin and atropin diminish the excitability of the vagus and cause a rise of blood pressure. Thyroiodin would, therefore, come ***nearest to the muscarin group.***

8. THERAPEUTICS.

(a) Conditions in which the Functions of the Thyroid Gland is Evidently Defective.—*Cachexia strumipriva, myxedema, sporadic cretinism, and some forms of goiter.* In these the benefit persists only so long as the administration is continued. The form of goiter which is most conspicuously influenced is hyperplastic follicular. Complete disappearance is the exception, but considerable decrease the rule, especially in young patients. Results are not permanent, and usually there is a relapse if the remedy is discontinued.

(b) Obesity.—Since in these cases the object is to reduce the fat and not the muscle, and since thyroid increases the metabolism in both, it must be joined with an abundant proteid diet, nor should its administration be continued a very long time. The opinions of its value differ, some clinicians claiming inconstant and temporary results.

(c) More obscure are its actions, if indeed they exist, in various *skin diseases:* psoriasis, eczema, lupus. Also very obscure are the reported benefits to *uterine fibromata* and menstrual disorders.

(d) Since it has been observed that thyroidectomy retards the growth of bone and the formation of callus after fracture, the administration of thyroid has been suggested for *slow-healing fractures.* It has not been sufficiently tried to allow definite conclusions.

(e) Thyroid administration has been suggested for chronic rheumatism, gout, arteriosclerosis, rickets, infantile cachexias, hemophilia, etc. It is doubtful whether it is of any real benefit in these conditions.

9. RELATION OF THE THYROID TO BASEDOW'S DISEASE.

The symptoms of this disease (exophthalmic goitre) suggest its causation by increased and perverted functionation of the thyroid gland (Mœbius, 1886). The metabolic changes are especially striking: the O and CO_2 metabolism is increased by 20 to 50 per cent.; the nitrogen excretion is also raised, but not to the same degree. The severity of these metabolic changes is generally parallel to the severity of the disease, and cannot be accounted for by the tremors, etc. These phenomena point plainly to thyroid hypersecretion. The chemic examination of the gland (Oswald, 1905) shows generally a decrease of thyreoglobulin, and this is poor in iodin. There is reason to believe that the paucity of the thyreoglobulin is due to its more rapid passage into the blood, and that the glands form even more than the normal quantity; but the low iodin content indicates that this is of poor quality. The disease therefore presents at once the phenomena of an excess and of a deficiency of thyroid secretion; the excess being indicated by the metabolism, the deficiency by the other symptoms. This can only be explained on the assumption that the thyroid secretes several active principles.

Antithyroid Serum.—Proceeding on the theory that Basedow's disease consists in a thyroid intoxication, Ballet and Enriquez (1894) attempted its treatment by the administration of the serum of thyroidectomized dogs, supposing that these produced substances antagonistic to thyroid secretion. In the same year, Lantz employed the milk of thyroidectomized goats, but this soon becomes repugnant to the patients. At present, the antithyroid serum is generally obtained from sheep. The experience with this serum has not been sufficient to warrant a final judgment of its value. It appears to act favorably in a considerable proportion of cases by palliating the symptoms; but it is not curative and other measures should not be neglected. It has also been tried in other nervous disorders, supposedly allied to this disease. The serum acts equally well by mouth and subcutaneously. The oral administration is preferred. It is not toxic.

9. SOME COMMERCIAL PREPARATIONS.

**Fresh Sheep's Thyroid,* preferably raw or broiled. ⅛ to ⅓ gland as dose.

**Thyroid Tablets* (0.13 Gm. = 2 grains).

Glandulæ Thyroideæ Siccæ (U. S. P.) [*Thyroideum Siccum* (B. P.)]. — The dried gland of the sheep = 5 parts of fresh. *Dose:* 0.1 to 0.6 Gm. (2 to 10 grs.) (0.25 Gm. = 4 grs., U. S. P.).

Liquor Thyroidei (B. P.). — 100 minims = one gland. *Dose:* 0.3 to 1 c.c. (5 to 15 minims).

**Iodothyrin* (Thyro-iodin). — The commercial preparation is a milk-sugar trituration, containing 0.03% I. Its *dose* is 1 to 2 Gm. per day.

**Antithyroid Serum.* — The blood serum of sheep whose thyroids were removed six weeks previous to the first venesection; marketed after the addition of a little phenol (*Mœbius Serum, Rodagen*) or dried (*Thyroidectin*). *Dose:* of the dry, 1 to 3 capsules of 0.3 Gm. (5 grains) three times a day; of the moist, 5 c.c. (teaspoonful) every second day in a tablespoon of wine.

III. PITUITARY BODY (HYPOPHYSIS CEREBRI).

The effects of extracts made from the anterior (hypophyseal) and posterior (infundibular) portions are quite different.

The ***infundibular lobe*** is the more active. It contains a pressor and depressor substance, the former soluble in salt solution and insoluble in alcohol and ether; the latter soluble in all these solvents. The pressor substance acts both on the heart and on the peripheral arteries; its action is prolonged, whilst that of the depressor substance is evanescent. The rise of blood pressure may be accompanied by cardiac slowing (Schaefer and Vincent, 1899). The injection of one dose diminishes the effects of subsequent injections (Howell, 1898).

The ***hypophyseal portion*** (which has a structure resembling the thyroid) produces a distinct fall of blood pressure, usually accompanied by acceleration and weakening of the heart (W. W. Hamburger, 1904). A second injection, following immediately on the first, is ineffective. This inhibition is due to the presence of a distinct substance.

The ***effects of excision*** of the gland resemble those of thyroidectomy, pointing to the importance of both to the circulation of the brain. These symptoms are usually relieved by injections of the extracts.

The gland is usually found atrophied in ***acromegaly,*** a condition of gigantic overdevelopment of the extremities, skull, tongue, nasal mucous membranes, etc., and by various visual disturbances; but a causal connection between these two cannot be considered as definitely proved. Nor have results of its therapeutic use in this disease been at all encouraging. The dried extract is used in doses of about 0.1 Gm.

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* Not official.

Study M. M. Lesson 23.

The oral administration of the gland produces no effect on the circulation; hypodermic injections cause some of the general effects, and considerable local vasoconstriction.

IV. LYMPHATIC GLANDS AND OTHER TISSUES.

All glandular organs, and perhaps all animal tissues, contain both pressor and depressor substances. The pressor principles predominate in saline extracts made at ordinary temperature, but are destroyed by boiling. The depressor substances are soluble in saline solutions and in alcohol or ether. They are not identical with cholin (Swale Vincent and Sheen, 1903).

Experiments with the injection of extracts of lymph-glands, spleen, thymus, bone-marrow, etc., have not yielded any definite results, and it is very doubtful whether they form any internal secretion. Bone marrow extract lowers the blood-pressure when injected intravenously (Brown and Guthrie, 1905).

The continued administration of these organs or extracts is said to *stimulate the production of blood corpuscles,* and they have been employed with varying success in the treatment of rickets, anemia, chlorosis, leucemia, tuberculosis, etc. Whatever action is possessed by them may perhaps be attributed to their content of nucleins. It has been demonstrated that these produce hyperleucocytosis.

These nucleins have of recent years been extensively tried for various obscure affections, and so far it is impossible to say anything definite about them. They are converted into xanthin bodies in the organisms. They are rich in phosphorus and are not destroyed by peptic digestion. Under the action of alkalies they are split into an albumin, and into *nuclei acid,* which latter retains the phosphorus. It is used in hemophilia (as also nuclein), and as a mild caustic. (It is claimed that it destroys diseased tissue, but leaves healthy tissue intact.) *Nuclein* is made either from yeast or from spleen. It occurs as a powder, soluble in weak alkalies. It is given by mouth in daily doses of 2 to 3 Gm. or subcutaneously as 1 c.c. of 0.5% solution.

Yeast has recently been recommended (by mouth and locally) against furunculosis. More extended observation is needed to establish its value.

V. PANCREAS.

Although this gland has for its most conspicuous function an external secretion, its internal secretion is none the less important. Its removal leads to *glycosuria,* with acetonuria, polyuria, great thirst, and hunger; in fact, conditions closely analogous to diabetes mellitus. This glycosuria occurs even when carbohydrates are withheld.

It can scarcely be considered as decided whether these effects are due to the absence of some substances produced in the pancreas or whether the cells of this organ are themselves necessary to the normal carbohydrate metabolism.

Recent experiments indicate that the pancreas produces a substance which, in conjunction with another substance found in muscle, causes the destruction of sugar, and that the removal of this pancreatic substance robs the body of the power of utilizing sugar. The cells of the islands of Langerhans seem to be particularly connected with the production of this substance.

While it does not seem improbable that some cases of *diabetes* in man are connected with disease of the pancreas, it must be confessed that administration of the powdered substance or extract has not been therapeutically successful in these conditions.

VI. PHLORRHIZIN.

This substance (often misspelled Phlorizin or Phloridzin) may be considered here, in want of a better place. It is a glucosid which occurs in the root-bark of the apple and other trees. Its administration leads to glycosuria, polyuria, acetonuria, and to a great increase of nitrogen excretion (to six times the normal).

Phlorrhizin Glycosuria.[1]— It will be seen that these effects, especially the glycosuria, bear a close superficial resemblance to those of pancreas excision; but the mechanism of their production is quite different. The phlorrhizin glycosuria differs indeed from all others in that the sugar content of the blood is not increased, even if the kidneys are excised, but may even be diminished. This disposes also of the suggestion that the glycosuria is produced by the sugar split off from the phlorrhizin. Indeed, it is doubtful whether the glucosid is decomposed in the body, for it is excreted largely unchanged by the urine; further, the sugar-free decomposition product, phlorhetin, also causes glycosuria. It has been suggested that the glycosuria is due to an increased permeability of the kidney cells to sugar (Von Mering). This would explain the phenomenon partly, although it is rather suggestive that the permeability to other substances (salts or proteids) is not affected. Pavy, Brodie, and Siau (1903) have shown that the quantity of sugar which is excreted when the other abdominal viscera are excised, exceeds the quantity of sugar which disappears from the blood. This forces the conclusion that *phlorrhizin causes the kidneys to assume the function of forming sugar from the proteids of the blood, and of secreting this into the urine, i. e.,* a function analogous to that of the mammary glands. It may be supposed that the sugar of the blood exists in loose and firm combination with the blood proteids; the phlorrhizin causes the kidney to secrete first the loosely combined sugar; and when the supply of this fails, the firmer combination is attacked. The stock of carbohydrates in the body therefor disappears first, although some glycogen is retained very persistently. At this time the D ÷ N quotient (dextrose divided by the nitrogen of the urine) is naturally variable, but high. On proteid diet and in starving animals it becomes constant (3.75 for dogs, 2.8 in goats and rabbits), just as in pancreatic diabetes, where the sugar is also formed from proteids. This accounts for the increased nitrogen excretion.

The excretion of sugar is proportional to the activity of the kidneys; it is diminished, for instance, when one kidney is excised, and increases again as the remaining kidney hypertrophies (Schilling, 1904). The glycosuria is said to be diminished in parenchymatous nephritis, and the injection of phlorrhizin (phlorrhizin test, 5 mg. in warm water, hypodermically) has been proposed as a means of diagnosis. The result, however, is not decisive in either sense. The administration of the drug itself causes necrotic changes of the renal cells.

The amount of glucose in the urine may be very high, above 12%.

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[1] Exercise 34.

It persists for several hours after a single injection, but may be prolonged indefinitely, at its highest degree, by administering 1 Gm. of the glucosid per kilo of bodyweight, by mouth, three times a day. Larger doses do not increase the glycosuria.

Phlorrhizin, as all measures which cause inordinate proteid metabolism, leads to fatty infiltration of the liver. The *acetonuria* also occurs in all similar conditions, and, like the production of oxybutyric acid, it results from the imperfect oxydation of fats, due to the disturbance of metabolism. The combined sulphuric acid of the urine is not increased. Albuminuria occurs rarely.

VII. ASPHYXIAL GLYCOSURIA.[1]

Two mechanisms for the production of glycosuria have just been described, viz.: Diminished activity of the pancreas (perhaps the suppression of an oxidizing ferment); and secretion by the renal epithelium (phlorrhizin). Glycosuria may also be brought about by another mechanism, viz., by an increase in the per cent. of sugar in the blood. This may be the result of introducing excessive amounts of carbohydrates into the body; but it may also be the result of an overabundant conversion of reserve glycogen into sugar. This occurs through stimulation of the glycogenic center in the medulla, by puncture, by stimulation of sensory nerves, by asphyxia, by whatever means this is produced; it seems also to be favored by cooling. This glycosuria is seen after CO, Curare, Strychnin, Morphin, Veratrin, Amyl nitrite, the volatile Anesthetics, Chloral, drugs which produce methemoglobin, such as the coal-tar products, etc. It also follows metallic poisons. Glycuronic acid and its compounds may in part replace the closely allied glucose.

VIII. KIDNEYS.

Even this organ, whose function is so conspicuously connected with external secretion, appears also to be charged with the function of internal secretion. This action is largely *metabolic;* removal of a large portion of the kidney increases the proteid waste of the body. It cannot be stated whether this is connected with a chemic substance.

Total excision of the kidneys produces a speedy death. This is due in part to the non-excretion of toxic organic and inorganic waste products. But it appears that the kidneys secrete a substance which is antitoxic to some of these poisonous products; for injection of kidney extracts, or of the serum from the renal vein, is said to delay the death. (Experiments of this kind need to be freely controlled before much weight can be attached to them.

Kidney extracts also have some action on the *circulation.* The effect on the isolated heart-muscle is comparatively small. It consists in lessened tonus, slight slowing, and increased amplitude. The blood pressure falls at first, then rises. These effects are not due to urea, which causes in the isolated heart a slight increase in the tonus, with some acceleration, and slight increase of force.

IX. SEXUAL GLANDS.

Extirpation of the sexual glands was amongst the earliest surgical operations, and thus it could not fail to be noticed that it is followed by very marked psychic and physical changes. But the subject was neglected therapeutically until the announcement by Brown-Séquard, in 1889, of the remarkable stimulating qualities which he noticed on hypodermic injection of orchitic extract.

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[1] Glycosuria and diabetes mellitus are not identical, diabetes being a disease in which glycosuria is only one of the symptoms.

This discovery was exploited in so sensational a manner that the whole subject was in danger of falling into discredit. While the somewhat extravagant claims of the discoverer must be considerably discounted, numerous independent observers have shown by the ergograph that it causes a marked *increase* (15% to 20%) of *power for voluntary muscular work.*

This action has been attributed by Poehl to the base *spermin* ($C_5H_{14}N_2$). While this is especially abundant in this extract, it also exists in many other tissues. Its actions on the heart and circulation resemble those of *cholin,* which is also present in the orchitic extract. Its phosphate forms the "*Charcot-Leyden*" crystals found in sputa, etc. The action of these substances is supported by a nucleoproteid, which causes a slowed heart and fall of blood pressure through stimulation of the vagus center, and dilatation of the splanchnic vessels, also through the center. The orchitic extract applied to the *isolated heart* (Porter and Langendorff method) shows increase in force and frequency.

Much more conspicuous, however, are the effects of the sexual glands upon *metabolism.* This was first observed clinically: After the climacteric or oöphorectomy, *obesity* occurs in about 40% of the cases. The excision of the testicles has much less effect. In addition to this increase of fat, the loss of the ovaries also brings with it a very characteristic train of phenomena, generally attributable to spasms of the vascular system.

The subject has recently been studied experimentally on bitches by measuring the heat production. A very marked decrease of this is found after the operation — i. e., oxidation and consequently carbon and hydrogen metabolism, are diminished. It is under dispute whether the excretion of phosphates is diminished or not.

This effect is abolished by administration of ovarian extracts by the mouth. In other words, ovarian substance *increases oxidation with the castrated animal,* even somewhat above the normal amount. On the normal animal on the other hand, it has no such effect.

Males show exactly the same phenomena, but much less marked. The spermatic extract has the same action as the ovarian on both sexes, but the ovarian is much more powerful.

The metabolic function of the ovaries is to some extent supplemented by the uterus. The diminution of heat-production does not reach its maximum until the uterus has undergone atrophy.

Administration of ovarian substance does not prevent atrophy of the uterus after excision of the ovary. (Loewy and Richter, 1899).

Therapeutically, ovarian tablets have been found quite successful in all the conditions following the functional loss of the ovaries. They have also been tried in chlorosis, but without decided benefit.

Extracts of the *mammary* and *parotid* glands have also been tried against uterine fibroids and ovarian tumors, but the beneficial results which have been reported can scarcely be accepted until further confirmation.

MATERIA MEDICA.

Testicular Extracts (from Bull or Ram):

* *Testes Siccati Pulv., Didymin, Testin, Testis.*— Dry glands or extracts. *Dose:* 1 Gm.

* *Spermin Poehl.*— 1 to 6 c. c. of 2% solution, hypodermic.
* *Succus e Testibus.*— Liquid preparation, 15 c. c.
Ovarian Extracts (Cow or Swine):
* *Oöphorin.*— A dry extract, ten times as strong as fresh ovaries. *Dose:* 1 to 2 Gm.
* *Parotida or Mammaria Sicca.*— 0.15 Gm. per day.
* *Ovariinum Siccum.*— Five times as strong as fresh glands.

X. SECRETIN.

Bayliss and Starling (1902) discovered that the maceration of the mucosa of the small intestine with dilute hydrochloric produces a substance, secretin, which stimulates the secretion of the pancreas. Secretin is not a ferment, since it is not affected by heating or alcohol. Its action is not hindered by atropin. The substance can scarcely be utilized therapeutically, since it is not absorbed from the intact alimentary canal and its hypodermic injection is painful. The latter may be justifiable to confirm the pancreatic connection of fistulæ. (Macleod, 1903.) (In life, secretin is probably produced *within* the cells, from which it may be absorbed.)

CHAPTER XIV.

APOMORPHIN; IPECAC; EMETICS.[1]

(A) APOMORPHIN.

This is a base formed by *dehydrating morphin* through the action of concentrated mineral acids:

$$\underset{\text{Morphin.}}{C_{17}H_{19}NO_3} - H_2O = \underset{\text{Apomorphin.}}{C_{17}H_{17}NO_2}$$

It has *lost almost all the narcotic action* of morphin and shows a further development of the excitant effects which were noted in the action of the former on certain animals. It shows in addition a depressing action on striped and cardiac muscle.

I. SUMMARY OF ACTIONS.

1. Irritation of the central nervous system, and particularly of the vomiting center in the medulla.
2. Depression of striped and cardiac muscle.

II. DETAILS OF ACTION.

1. The irritation of the central nervous system is exerted first and mainly upon the **vomiting center**, its action being so specialized that small doses give rise purely to emesis without developing any other direct action.

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* Not official.

[1] Exercise 30.

The vomiting is preceded by the classic **symptoms of nausea,** which must not be ascribed to a direct action of the drug. They are: a feeling of sickness, lassitude and weakness, increased secretion of sweat, saliva, mucus, and tears, a sensation of warmth. *During the act* of vomiting there is also an increase of respiration and pulse, and of blood pressure.

The nausea symptoms are also obtained from doses too small to produce vomiting (1 to 2 mg. every two hours by mouth).

With the usual hypodermic dose (5 to 10 mg.—$^1/_{12}$ to $^1/_6$ grain) vomiting occurs in man usually inside of *fifteen minutes,* and the nausea usually disappears very quickly; it may, however, persist for some time and the vomiting be repeated. Even *collapse* may occur, simply as the result of the vomiting, and not as a direct effect. It is not dangerous in normal individuals.

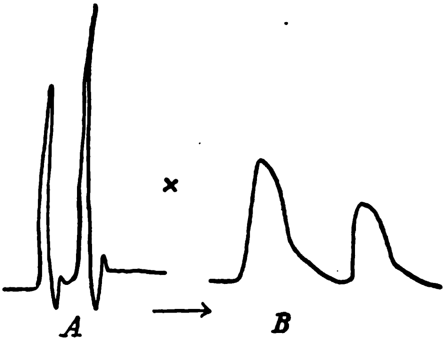

Fig. 65.—Apomorphin on frog's muscle. Make and break shocks: *A,* Normal; *B,* after lying in 1:500 apomorphin. The contractions are lowered, the relaxation lengthened, and the muscle is very quickly fatigued.

The vomiting with apomorphin is mainly of *central origin.*

The fact that it occurs more quickly and with a smaller dose if the drug is administered hypodermically than when it is given by stomach would point to this. And even more direct proof can be furnished: After the blood-vessels supplying the stomach have been ligatured, apomorphin does not produce vomiting when placed in this organ, but acts when injected into the general circulation (from which it cannot reach the stomach). Its central action is, however, supported very slightly by a *local* one, since it causes weak contraction in the excised stomach; but this plays a very subordinate rôle.

2. If the drug is taken in *very large doses,*—and especially by **animals which are incapable of vomiting,**[1]—it exhibits its irritant effects upon the rest of the central nervous system. It causes great restlessness with circus movements, excitement, and terror. The respiration is quickened. Convulsions set in and death occurs through paralysis of respiration. These general irritant effects are never purposely produced in man, and are rarely witnessed. Very minute doses (up to 2 mg. in man) are slightly hypnotic.

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[1] Fish, frog, toad, and lizard vomit easily in certain seasons (June and July best, January and February worst), if the stomach is filled with food.

3. The irritability of **striped muscle** is much diminished and finally abolished by it in frogs (Fig. 65), but this action has not been shown in *mammals:* the muscular weakness witnessed in the latter depends purely upon the nausea.

4. A similar action is shown on the **cardiac muscle:** it stops the heart even after atropin.

5. It paralyzes nerve-cells and ganglia on direct application.

III. TOXICOLOGY.

The toxicology of apomorphin is not important. It is not *excreted* into the stomach like morphin, but is probably decomposed in the organism.

Quebrachin, aspidosamin, quebrachamin, and *aspidospermin* have a similar action, but vomiting is not so prominent a symptom.

IV. MATERIA MEDICA.

Apomorphinæ Hydrochloridum (U. S. P., B. P.), $C_{17}H_{17}NO_2.HCl$.—Grayish powder, sol. 39.5 water, 38.2 alc. As an emetic, 5 to 10 mg. (1/12 to 1/6 gr.) are given hypodermically in 1% solution. As an expectorant, 2 mg. per mouth. (U. S. P.: Expectorant, 2 mg.=1/30 gr.; Emetic, 5 mg. = 1/10 gr.).

The solutions become *green* in the light, but this change does not greatly lessen their activity.

Injectio Apomorphinæ Hypodermica (B.P.).—1%. (To be freshly prepared.) *Dose:* 0.3 to 1.0 c. c. (1 to 15 minims).

Therapeutic Uses.— See end of chapter.

Apocodein, the corresponding derivative of codein, preserves the convulsant action, but in addition it paralyzes all nervous structures, the endings as well as the central cells. In the successive stages of its action it affects the terminations of the vagus, vasomotors, and the nerve endings of all smooth muscle, striped muscle, and cardiac accelerator. It has proved very useful in pharmacologic experimentation, to distinguish whether a peripheral stimulation affects the endings or the cells; for it does not paralyze the latter (Dixon, 1903).

Aspidosperma (Quebracho), the bark of Aspidosperma Quebracho-blanco, contains six or more alkaloids with very similar actions. These resemble apomorphin; one of the alkaloids, aspidosamin, produces emesis; the others only cause nausea, with its usual accompaniments. The drug also shares the other central and peripheral actions of apomorphin. Moderate doses stimulate the central nervous system, particularly the medulla, and increase the respiration. Larger doses depress the respiratory and vasomotor centers, and depress the cardiac and skeletal muscles (Harnack and Hoffmann, 1884; Wood and Hoyt, 1903). The fluidextract, in doses of 1 to 4 c. c. (¼ to 1 ʒ) has been

All birds vomit, but from the crop, and not from the stomach. Hogs vomit with difficulty. Other animals with paired hoofs, insect-eaters and carnivorous, vomit easily. Animals with odd hoofs, ruminants, and rodents cannot vomit, although large does of emetics may cause salivation and nausea. It is well known that young children vomit very much more easily than adults.

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recommended as expectorant and in dyspneic conditions, but is rarely used.

B. IPECACUANHA.

I. CONSTITUENTS.

Ipecac contains three alkaloids: emetin, cephaelin, and psychotrin, and a tannin, ipecacuanhic acid. Emetin and cephaelin, which agree qualitatively in their actions, appear to be solely responsible for the effects of the drug. Psychotrin is present in too small amount to be important.

The **ipecacuanhic acid** was, until recently, considered a bearer of the valuable action of ipecac in dysentery, and a preparation of the drug, deprived of its alkaloid, was recommended for use in this disease. It has been shown, however, that this tannin is inactive. The ipecacuanhic acid possesses *all* the chemic characters of caffeotannic acid (see Index), from which it differs only by one atom of oxygen. The pharmacologic actions of these two tannins also agree perfectly (and differ from ordinary tannin) as they are neither antiseptic nor astringent (Kimura, 1903).

II. SUMMARY OF ACTIONS OF EMETIN AND CEPHAELIN.

1. A strong local irritant effect on mucous membranes, exerted particularly on the alimentary canal, resulting in vomiting and diarrhea.

2. Excitation with following paralysis of the central nervous system.
3. A weak apomorphin action on striped and cardiac muscle.

III. DETAILS OF ACTION.

The phenomena of **vomiting** and nausea are the first and most prominent symptoms, and present the clinical picture described under apomorphin. The emesis is produced largely, if not solely, by the local irritation, although it is difficult to exclude the possibility of cooperation by the vomiting center. The effect occurs quite as promptly when it is given by mouth as when it is used subcutaneously. The nervous path is also the same as with local, irritant emetics.

According to Openchowski, there is reason to believe that the centrally acting emetics (apomorphin, lobelin) do not act on the same center as the peripheral emetics (ipecac, copper, antimony, etc.), and that the efferent impulses take a different path. That for the central emetics involves the corpora quadrigemina, spinal cord to fifth dorsal, and splanchnics; no vomiting occurs if any of these are destroyed; but it is not prevented by dividing the vagi. With the locally acting emetics, including ipecac, the conditions are reversed: vomiting is prevented by section of the vagi, but not by dividing the splanchnics, etc. (Magnus, 1903).

With ipecac, emesis is *produced much more slowly* than in the case of apomorphin, and the *nausea* is in consequence more prolonged. Ipecac increases the *tracheal secretion,* even when given intravenously.

If the drug has been given by the stomach, it is usually voided by the vomiting, in which ease there may be no further symptoms; but if it was administered *hypodermically,* the vomiting is followed by **diarrhea,** which is often bloody, by nephritic albuminuria, and by depression of the heart.

Central symptoms make their appearance after large doses.

Paralytic symptoms set in, among the earliest in mammals being *vasomotor paralysis* with fall of blood pressure. This is further aided by *weakening of the heart muscle* due to its direct muscle-action, and this results in *death.* If the action has lasted any time, the autopsy will show a marked *gastro-enteritis,* with ecchymoses and even ulcers.

Edema of the lungs, from the hypersecretion of mucus and the weakened heart, is sometimes seen.

The **local irritation** is one of its important effects. It may give rise to conjunctivitis, bronchitis, pustular eruption on the skin, etc., according to the place to which it has been applied.[1] On hypodermic injection it is very apt to produce local *abscesses,* and more remotely the gastro-enteritis already mentioned. The irritant action on subcutaneous tissue is, however, comparatively weak since the alkaloids are rapidly removed by the circulation. The occasional nephritis is to be referred to the irritant action.

In smaller quantities it produces, especially when given by the mouth, a moderate congestion of the *gastric mucous-membrane,* which may be very desirable in the treatment of some *dyspepsias;* and it also influences the intestinal mucous membrane in a favorable manner in *tropical dysentery.*

Subcutaneous *administration* is inadmissible on account of the danger of the systemic actions. To make the effect as purely local as possible, the crude drug, or its preparations, are used to the exclusion of the isolated alkaloids. As emetic, the powdered ipecac deserves the preference. For the nauseant action it has been recommended to use an infusion by gargling.

IV. COMPARATIVE ACTION OF EMETIN AND CEPHAELIN.

The composition of the alkaloids differs merely by two CH_2 molecules (Emetin $= C_{30}H_{44}N_2O_4$; Cephaelin $= C_{28}H_{40}N_2O_4$); their action is accordingly similar, but some minor differences are of therapeutic importance: *Emetic effect:* Cephaelin is by far more emetic, whilst emetin is the better nauseant. *Cardiac effect:* Emetin is much more depressing. *Kidneys:* Cephaelin is more irritant. *Blood corpuscles:* Cephaelin is somewhat hemolytic (Paul and Cownley, 1901; Lowin, 1902; Wild, 1805; of the older papers, Podwyssotzki, Arch. exp. Path., 11:231, 1879).

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[1] Some persons are so sensitive to the local action of ipecac that the opening of a jar at a distance of several feet will produce violent sneezing and discomfort.

V. MATERIA MEDICA.

Ipecacuanha (U. S. P., B. P.).—The root of *Cephælis Ipecacuanha*, Rubiaceæ. Brazil and Colombia; cultivated in India.

Two varieties are found on the market, called Rio and Carthagena Ipecac. The B. P. recognizes only the former, the U. S. P., both. Recent researches have shown that the Carthagena variety contains more of both alkaloids, but particularly of Cephaelin, and is therefore the more valuable.

Principal constituents: Besides the active ingredients enumerated, there are starch, volatile oil, etc. The total alkaloids amount to 2.7 to 2.9% (at least 2% U. S. P.). The ratio of emetin to cephaelin varies from 3 emetin : 1 cephaelin in Rio to ⅔:1 in Carthagena.

Pulvis Ipecacuanhæ: *Dose:* As emetic, 1 to 2 Gm. (⅓ to ¼ teaspoonful) in lukewarm water (U. S. P.: Expectorant, 0.065 Gm. = 1 gr.; Emetic, 1 Gm. = 15 gr.).

Simple Preparations:

Fluidextractum Ipecacuanhæ (U. S. P.).—¾ alcohol; 1.75% alkaloids. *Dose:* Expectorant, 0.05 to 0.3 c. c. (1 to 5 ♏); emetic, 2 c. c. (30 ♏) (U. S. P., 0.05 c. c. = 1 ♏; 1 c. c. = 15 ♏).

Extr. Ipecac. Liq. (B. P.).—Alcohol; 2.25% alk. *Dose:* as the preceding.

Syrupus Ipec. (U. S. P.).—7% of fldext.; contains acetic acid. *Dose:* As expectorant, 1 c. c. = 15 ♏; as emetic, 15 c. c. = 4ʒ (U. S. P.).

Vinum Ipec. (U. S. P.).—10% of fldext. *Dose:* As expectorant, .05 to 2 c. c. (10 to 30 ♏) (1 c. c. = 15 ♏, U. S. P.); as emetic, 15 c. c. (4ʒ).

Vinum Ipec. (B. P.)—5%; 0.1% alkaloids. *Dose:* twice the preceding.

Acetum Ipecacuanhæ (B. P.).—As the wine.

Compound Preparations:

Pulvis Ipecacuanhæ et Opii (U. S. P.) [*Pulvis Ipec. Compos.*, B. P.]. *Dover's Powder.*—10% of each active ingredient. *Dose:* 0.05 to 1.0 Gm. (1 to 15 grs.) (0.5 Gm. = 7½ gr. U. S. P.).

Trochisci Morphinæ et Ipecacuanhæ (B. P.).—Each contains 1/40 grain (0.0016 Gm.) of morphin hydrochlorate, and 1/12 grain [0.005 Gm.] ipecac.

Tinctura Ipecacuanhæ et Opii (U. S. P.).—Contains 10% of each. *Dose:* 0.2 to 1.2 c. c. (3 to 20 minims) (0.5 c. c. = 8 ♏, U. S. P.).

(C) THERAPEUTICS OF EMETICS.

I. PHYSIOLOGY OF VOMITING.

The act of vomiting consists in an upward emptying of the stomach, produced by a contraction of its walls and its compression by the abdominal muscles, joined with a simul-

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taneous closure of the pyloric and relaxation of the cardiac sphincters. When the compression of the organ and relaxation of the sphincter do not occur simultaneously, *retching* results, the contents being retained. This frequently precedes the vomiting. A still earlier stage presents the phenomena of nausea as already detailed. The act of vomiting is a reflex one, and to some extent physiologic, especially in young children, where it has little more significance than sneezing. It is controlled by a nerve-center, situated in the proximity of, and closely related to, the respiratory center. The reflex arch might be stimulated at any part of its course, and vomiting thus produced. The *center* may be directly affected by concussion or pressure on the brain, and by drugs which we will call "*central emetics.*"

The *reflexes* may take their origin in many organs: from the alimentary canal — pharynx, stomach, and intestine; from the special senses — by sight, smell, or taste; but in these cases the effect results more strictly from a psychic cause than directly from the sense organs. Disturbance of the mechanism of equilibrium is also an effective cause, as in vertigo and sea-sickness. The impulses may also arise in the gall-duct, kidney, ureter and bladder, sexual organs, etc.

Such irritation may be obtained by any of the known forms of stimulation, and consequently also by drugs, the alimentary canal being the most convenient point for attack. We will call drugs acting in this way *local emetics*. There is still another type of local emetics conceivable, namely, those which should *act directly upon the muscular walls* of the stomach without the intervention of the reflex mechanism. But since contraction of the stomach alone does not usually result in vomiting, and since, further, all the drugs which produce this irritation also produce at the same time a reflex irritation, they may well be considered with the last class. We have, then, according to their seat of action, two classes of emetics — local and general.

Emetics do not operate in deep narcosis. A large dose of morphin may be utilized in dogs to prevent the vomiting of irritant drugs. These are given shortly after the emesis produced by the morphin itself.

II. ENUMERATION OF EMETICS.

Any irritant substance may act as a *local emetic* when brought in contact with the lining of the alimentary canal, and especially of the stomach. The number of irritant substances is very large — they include practically everything; even water in sufficiently large quantity has this effect, especially when warm, and is indeed used as an adjunct to other emetics (its effect being, however, largely mechanical). Besides the substances which have specific irritant properties, those otherwise inert may irritate by their salt action if they are soluble, or by their mere presence if they are not.

Of course, these actions are in very many cases not strong enough to produce even a trace of nausea; nevertheless, the number of substances which may produce emesis, either by their local or general action, affords a very large material, the greater part of which is valueless for practical use, since vomiting forms only one factor in their action. However, it has been possible to select a comparatively small number which show freedom from other actions. It should further be said that very many of the substances which we are now to consider have a central action as well as a local one.[1]

Amongst **local emetics** we have: *1. All salts, and especially the metallic salts.* Especially ZINC and COPPER SULPHATE and **Tartar Emetic** and AMMONIUM CARBONATE.

2. *Those acting on muscles or centrifugal nervous mechanism:* Nicotin, Morphin, Pilocarpin, *Sanguinaria*, Phytolacca, Lobelin, Muscarin, Physostigmin, etc.

3. *Organic irritants:* **Ipecac,** *Senega,* MUSTARD, *Quillaja,* Digitalis, **Squills,** Quinin, Carbolic Acid, etc.

Of **general emetics,** APOMORPHIN is the main representative.

III. USE OF EMETICS.

Emetics are used for two very different objects: to *produce vomiting or to produce nausea.* The same drug will accomplish either object, according to the dose, the dose for nausea being about one-tenth of the emetic dose.

The several drugs are especially adapted to one or the other purpose, and it is well to make a selection accordingly.

The indications for the use of emetics were formerly very numerous and general, but they are now obsolete except for very definite objects.

1. **The nauseant stage** is used mainly in the treatment of catarrhal conditions and *coughs.* The *increase of secretions,* especially mucus, is the desired feature in this, and they are only useful when the mucus is deficient or thick and tenacious.

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[1] Italics signify that the drug is used mainly as nauseant; small capitals, as emetic; heavy-face type, for both purposes.

Since the nauseant stage is to be prolonged without reaching actual vomiting, the milder emetics are chosen, and unless there is fever, those having the least depressing action on the medullary centers.

The doses given are calculated to be repeated every two hours.

The most important amongst these are:

Ipecac (in the form of wine or syrup, 15 ♏ (1 c. c.), or Dover's powder, 2 grs. (0.15 Gm.), the latter also useful on account of its diaphoretic action).

Saponin (in the form of Syr. Senegæ, ʒss — 2 c. c.): This has the advantage of not being absorbed and hence is less depressing.

Ammon. Carbonate (2 grs.— 0.15 Gm.): This is actually stimulating and on account of its alkalinity tends to dissolve the mucus.

Tartar Emetic (1 gr.— 0.06 Gm.): This is much more depressing, and if long continued may be absorbed and produce symptoms analogous to arsenic. Perhaps the best way of administering it is in the *Comp. Syr. Squills,* 15 ♏ (1 c. c.).

2. Actual Emesis.— (A) The **indications** for an actual emetic action may be summarized as follows:

1. To *remove solid bodies* from esophagus, pharynx, or upper air-passages. (If the obstruction is in the trachea, this is not without danger, since the body may become lodged in the glottis.) *Croupous membranes* may be removed in a similar manner. Emesis may cut short an attack of asthma.

2. *To empty the stomach:* (*a*) When the food is not being digested, especially after overeating.

(*b*) *To remove poisons:* This is of especial importance in acute poisoning through substances administered by the stomach, but it may even be useful when the poison has been administered in other ways, especially in the case of morphin, when the poison is excreted into the stomach. They are useful in the same way in chronic intoxications, and a beneficial action which has been claimed for them in malaria and other fevers may perhaps be partly explained in this manner. Ipecac is especially useful for the latter purpose, since it also produces diarrhea.

Their use in acute poisoning may often be replaced by the stomach-pump and by lavage. They should be avoided

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when the poisoning is due to caustics, since the violent compression is apt to cause rupture of the weakened wall of the stomach (this objection is perhaps rather theoretic). In many cases the poison itself causes emesis, so that further measures, except perhaps warm water, are unnecessary.

3. To cause *compression of the liver,* for the removal of bile and small gall-stones from the gall-bladder and ducts: The usefulness of this measure is perhaps doubtful; since the intestines are also compressed, the added vis a tergo cannot be very effectual, and on the other hand it might rupture a distended gall-bladder.

(B) The **contraindications** to emetics are mainly due to increase of pressure and to debilitation, and are as follows:

1. Severe *heart-defects,* or *aneurysm* of the aorta, since the sudden and violent increase of intrathoracic and intra-abdominal pressure may result in the rupture of these organs.

2. *Atheroma.* The sudden changes in blood pressure are apt to burst a vessel and produce apoplexy.

3. Similarly, they may lead to hemorrhages in *phthisis.*

4. Abortion may result, in *advanced pregnancy.*

5. Tendency to hernia.

6. In all debilitated conditions there is danger of collapse.

7. Caustic poisoning.

(C) The **measures most commonly adopted to produce emesis** are the following:

1. *Warm Water, Tickling of Fauces.*— These do not usually act as emetics when the stomach is normal; but when it is irritable — as is usually the case when emetics are indicated — they may be sufficient. But on account of their uncertainty they are usually only employed to aid the action of other emetics.

2. The same may be said of *mustard* (a teaspoonful in a cup of hot water).

These means (1 and 2) do not cause much depression, but they act slowly and are uncertain; they are hence of value for *emptying the stomach* of food, etc., but would ***not be indicated in poisoning*** where a prompt action is the first requirement. When no other emetic is at hand, they should of course be tried.

3. *Salts of Alkalies.*— A concentrated solution of any neutral salt may cause vomiting through irritation, but they

are uncertain and have no advantage, with the exception of *ammonium salts.* These have a stimulating action on the medulla, tending to counteract the depression incident to nausea; they should be used whenever the depression is especially contraindicated. Their action is too slow and uncertain to be of use in poisoning. Ammonium *carbonate* has the additional advantage of dissolving mucus, and has its special indication in catarrhal conditions. It is given in doses of 10 to 20 grs. (1 Gm.) in solution, repeated until vomiting occurs.

4. *Metallic salts.*— Those in practical use are the Sulphate of Copper and of Zinc, and Tartar Emetic. The last may be to some extent absorbed, and is then very depressing; it is also very slow, so that it may be doubted whether it is ever indicated. Of the former, the preference is given to the copper salt, although the zinc sulphate has precisely the same action. They irritate in a specific manner those structures in the stomach which set up the vomiting reflex, before the protoplasm of the gastric wall has undergone any noticeable change. They are not absorbed so long as the mucous membrane is intact, and are hence quite safe. Their action is rapid, so that there is *no time for nausea.* The depressing action is also small. But they produce practically always some irritation of the gastric walls, and this limits their use to such cases of poisoning in which the poison is not injurious to the stomach itself. They must be especially avoided when there is reason to suppose that the mucous membrane has been injured, since they would be absorbed in this case and cause poisoning. Their only *advantage over apomorphin* consists in a less degree of nausea and depression. Copper sulphate is of especial value in *phosphorus-poisoning* if any of the poison is still in the stomach, since the metallic copper is precipitated and forms an impermeable coating over the unabsorbed phosphorus particles. It is administered in about 1% solution, 5 grs. (0.3 Gm.) repeated at intervals.

5. *Vegetable irritants,* including emetin, saponin, digitalin, etc., act slowly and manifest other actions, which practically limit their use to the production of nausea. Ipecac is sometimes used as an emetic (ʒj — 4 c.c. — of wine every fifteen minutes); or as the powder, 1 Gm., in lukewarm water.

6. Of *alkaloidal emetics,* not local irritants, *apomorphin*

is alone used in practice. It is indicated whenever a prompt emetic is desired. The only exception is formed by cases in which depression is especially contraindicated; in these, ammonium carbonate should be chosen for slow, copper sulphate for quick, action. Apomorphin is the only emetic which can be given hypodermically, and must therefore be used in all cases where swallowing is impossible. It is used in 1% solution hypodermically, in doses up to $\frac{1}{8}$ grain (0.01 Gm.) (or 1 c.c. (15 minims) of this solution).

CHAPTER XV.

ACONITE; VERATRIN; COLCHICIN; CARDIAC DEPRESSANTS.

(A) ACONITE GROUP.

I. COMPOSITION, ETC.

Aconite ushers in a series — comprising also veratrin and colchicin — characterized by widespread and confused stimulation and paralysis of nervous structures, both central and peripheral, and, in addition, by a peculiar action on skeletal and cardiac muscle.

Aconite itself is one of the oldest known poisons. It was employed (as the expressed juice) by the Greeks and Romans. The ancient Chinese and Gauls used it as an arrow poison. Its therapeutic use is of much more recent date (it was introduced by Störck in 1762).

The isolation of its toxic alkaloids (aconitins) is quite a recent achievement. Their preparation in pure form is very difficult, as they are easily decomposed into much less active hydration products. The *aconitins* are esters of closely related bases (aconins) and aromatic acids, especially benzoic acid. The most important are:

1. *Aconitin,* from Aconitum Napellus. (It is a benzoic acid-aconin.) The *Japaconitin,* from Ac. Japonicum, formerly supposed to be a distinct alkaloid, is now generally considered identical with aconitin.
2. *Pseudaconitin,* from Ac. Ferox.
3. *Delphinin,* from Delphinium Staphisagria.

The first and second seem to be about equally active; the third is considerably weaker.

The exact chemic structure and composition of these alkaloids are still quite obscure. They agree in giving hydration products which have qualitatively the same action, but are the weaker the more they are hydrated. (Pikraconitin is already only $^1/_{30}$ as strong as aconitin; aconin, $^1/_{2000}$).

$C_{32}H_{43}NO_{12}$[1] $+ H_2O = C_{25}H_{39}NO_{11} + C_7H_6O_2$
Aconitin Pikraconitin Benzoic Acid
$C_{25}H_{39}NO_{11} + H_2O = C_{24}H_{37}NO_{10} + CH_3OH$
Pikraconitin Napellin Methyl Alcohol
$C_{24}H_{37}NO_{10} + H_2O = C_{22}H_{35}NO_9 + C_2H_4O_2$
Napellin Aconin Acetic Acid

Commercial "Aconitins" usually represent mixtures of varying strength, some being a hundred times more active than others. This enormous variability is most unfortunate in a substance of so great a toxicity; and several fatal accidents, to which it gave rise, have led to the practical abandonment of the internal use of aconitin in therapeutics. The tincture, indeed, gives quite satisfactory results; but in regard to this it should be remembered that *the strength of the U. S. P. tincture has been reduced from* 35% *to* 10%; and that it is still twice as strong as the B. P. tincture.

II. SUMMARY OF ACTIONS.

1. Excitation and subsequent paralysis of many different nerve endings — sensory, motor, and secretory.
2. Excitation and subsequent paralysis of certain parts of the central nervous system.

Aconitin is the *most toxic of all alkaloids,* and is only surpassed by some of the toxalbumins and similar substances. Three milligrams are fatal to man.

III. DETAILS OF ACTION.

(A) Peripheral.— 1. The first effect of aconitin — whether on local or systemic administration — consists in a **local irritation** of the *sensory nerves* of the skin and mucous membranes. When applied to the skin in *watery* solution it has very little action, since it cannot be absorbed; but if it is dissolved in *oil,* it causes a pricking, itching, and burning; then, similarly to cocain, a total *paralysis of sensation* to touch, temperature, pain, etc. Applied directly to any kind of nerve-fiber, it destroys its irritability, and the recovery from this is quite slow.

These skin effects also follow its administration by mouth or hypodermically, but in the former case are preceded by similar phenomena in the mouth. There is the same tingling and burning, a *bitter-sour taste,* and disagreeable scratching sensations in the pharynx. Other mucous membranes are also affected and give rise to reflexes (sneezing, coughing, salivation, nausea, vomiting, etc.), which greatly complicate the picture of the intoxication. The irritation is in all cases followed by anesthesia. There is no *reddening* or other sign of inflammation (as there is with most local irritants), even on the mucous membrane.

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[1] This formula is not universally accepted, and is given here simply as an instance.

The great number of structures irritated when the drug acts from the blood would favor the theory that the stimulation is central; but this is disproved by the fact that the action is first seen in the situation where the aconitin is applied.

A peculiar and characteristic effect of aconite, a *chilly sensation* which occurs before either the temperature or the circulation through the skin is changed, must be due to a stimulation of certain temperature nerves, and is of interest, since aconitin seems to be the only drug having this action from the blood, although possibly some bacterial poison may also possess it. (Menthol also stimulates these nerves, but only on local application.)

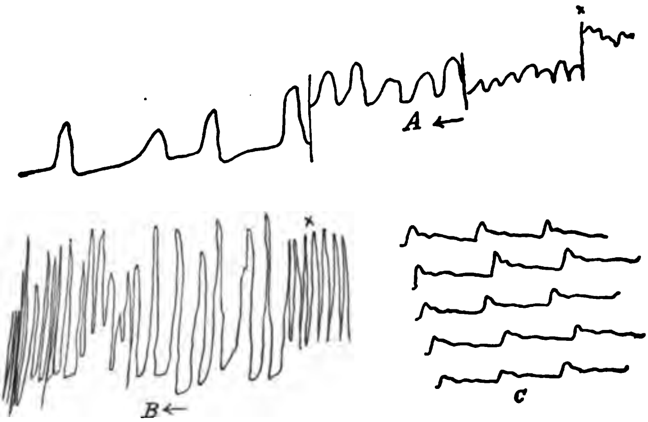

FIG. 66.—Aconite action begins at ×: *A*, Carotid pressure, dog; shows progressive vagus stimulation; *B*, cardiomyogram, dog; shows the stages of slowing, irregularity, and final quickening; *C*, sphymogram, man: the first line is normal; the others show the lowering of the pulse-wave.

2. The **secretory endings** in general are also stimulated, both directly and reflexly.

Striped muscle shows fibrillary twitchings, which persist after sections of the nerves, but are abolished by curare, and are therefore caused by stimulation of the endings. Larger doses paralyze the **motor endings.** Delphinin has even been recommended as a substitute for curare in laboratory work on frogs (Schiller, 1904).

(B) Action on the Circulation.[1]—*Therapeutic doses of aconite* slow the heart (Fig. 66 *A*), and thereby lower the blood pressure. The pulse consequently becomes soft and dicrotic (Fig. 66 *C*). The slowing (which is often absent in dogs) is due to stimulation of the vagus center; for it does not appear if the vagi have been divided.

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[1] Exercises 52, 59 and 63

This is as far as the action progresses with therapeutic doses. *Toxic doses* greatly increase the force and especially the rate of the heart, at the same time rendering it extremely arythmic (Fig. 66 *B*). The beats may occur in groups, as with digitalis. The heart finally goes quite suddenly into delirium cordis, and stops. During the earlier stages of this action the blood pressure is extremely variable, according to the varying force of the heart, and the successive stimulation and depression of the vasomotor center. Toward the later stages, the pressure drops severely (Matthews, 1897).

These cardiac effects are due partly to stimulation and depression of the vagus and accelerator mechanisms, but mainly to direct action on the cardiac muscle: the excitability of the latter is greatly increased, somewhat as with digitalis (which see). The quickening occurs even in the nerve-free heart of the embryonal chick; in mammals also it is seen after all the nerve endings in the heart have been paralyzed by apocodein.

The *isolated mammalian heart* (Hedbom-Langendorff) shows the following: The first effects are inconstant; the frequency is then enormously increased and amplitude lessened below what is accounted for by the quickening (increased irritability and weakened muscle). Then follows a transient increase of amplitude (muscular stimulation), and then sudden stoppage of left ventricle (paralysis of automatic property). The right ventricle and the auricles make a few more contractions. Caffein may start a few beats.

The actions of aconite on the frog's heart are very interesting and characteristic.[1] The phenomena are usually somewhat as in Fig. 67; their most satisfactory explanation is as follows:

1. Quickening, from stimulation of the accelerator endings and cardiac muscle.
2. Accelerator paralysis, beginning stimulation of vagus and beginning paralysis of heart-muscle. These result in slowing, and finally stoppage in 3. In 4 the vagus stimulation is giving place to paralysis, but the paralysis of the cardiac muscle has progressed so that the beats are weak and irregular. The irregularity may take various forms: often the blood is pumped from one side of the ventricle to the other, etc. It appears that the force of the heart is diminished, but that its excitability is increased. The rhythmic property is the next to give out; in consequence the heart stops, but it still responds to direct stimulation. This, too, is finally lost through paralysis of the muscle-fibers.

Considering the number of mechanisms involved, it need not surprise that the phenomena are not always typical, as here described.

(C) Central Nervous System.— The central actions of aconite appear extremely complex if it is attempted to study them in detail; but they become simpler if certain general facts are borne in mind.

The central nervous system is affected through its *whole extent, both directly and reflexly*. The *direct action pre-*

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[1] Exercise 49 (Boehm, 1871).

dominates and is *mainly paralyzing.* The action is exerted mainly upon the *medulla,* then comes the *cord,* and lastly the *hemispheres.* Consequently the *intelligence* remains unimpaired as a rule, but there may be *unconsciousness* as a consequence of *collapse.* The latter, which occurs early, is the result of *paralysis of the medullary centers.* Of these, the respiration is affected early; it becomes slowed, difficult, and dyspneic. This is partly reflex, from stimulation of the vagus endings in the lungs, etc. Paralysis of the respiratory center forms the *cause of death.* Of *other medullary* structures the vagus and vasomotor centers have been considered.

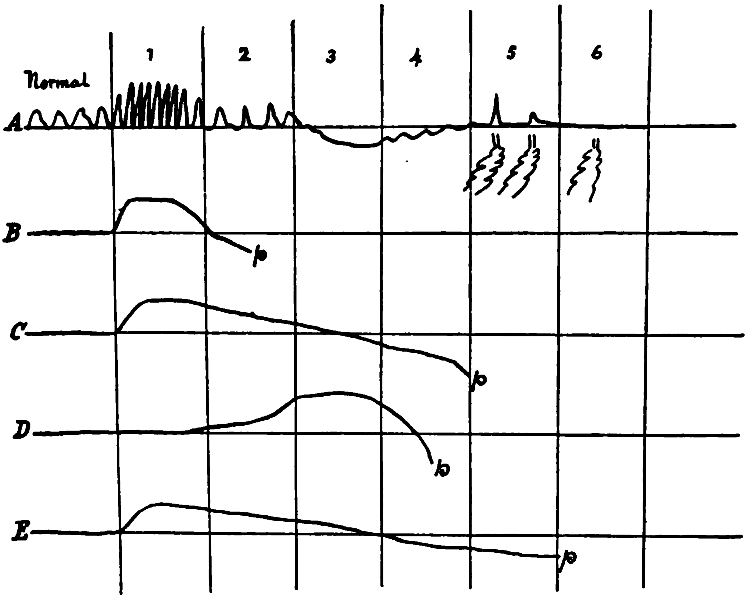

FIG. 67.—Schema of action of aconite on frog's heart; *A* represents diagrammatically the changes noted in the heart; electrical stimulation produces single contractions at 5, no response at 6. *B* to *E* are to show the part which the different structures of the heart contribute to the observed phenomena; a rise above the base line is to indicate increased functional activity, and the converse; *p*, point at which paralysis occurs; *A*, normal; *B*, accelerator endings; *C*, *rhythmic* property; *D*, vagus endings; *E*, muscle contractility.

The *vomiting, diarrhea,* etc., may also be due in part to direct stimulation of the centers, but are largely from local irritation.

Convulsions occur; their seat is probably diffuse. The *temperature* falls, both in health and disease, but this is probably an expression of the collapse action.

IV. TOXICOLOGY.

It will be seen from the above that the picture of aconite-poisoning must be a very *complicated* one; the whole nervous system, central and peripheral, being affected, in no well-defined order, in two diametrically opposed directions, the result must be extremely variable, and can be understood only by bearing this diversity in mind.

Accidental poisoning from the fresh plants,— which as monk's-hood or larkspur are quite common in gardens,— as also from liniments, etc., is quite frequent. On account of the small dose, the absence of postmortem signs, and the difficulty of chemic proof, aconitin has recently become quite a favorite for *suicidal* purposes. The use of the plant for *criminal poisoning* is widely spread in the East. The symptoms are so unmistakable — especially the tingling — that it has not found many users in civilized countries.

Symptoms.— In very large doses death may occur almost instantly — probably from paralysis of the heart. In sublethal doses the tingling, the slow, weak, and irregular heart, and the muscular weakness are most conspicuous. In moderately toxic doses the following picture is seen: *Burning* in mouth, stomach, and skin; excessive salivation; nausea, retching, *vomiting,* and *diarrhea* (both central and reflex effect). The burning passes into anesthesia. There is great restlessness. The *pulse* is slow, feeble, and arhythmic; later it may become very rapid. *Respiration* is dyspneic. There are muscular weakness, incoordination, vertigo. The *skin* is cold and livid. The *pupils* are usually dilated, from the asphyxia and convulsions. The *intelligence* does not usually suffer, but there may be stupor and even unconsciousness. The special senses and speech may be impaired. *Convulsions* are common. *Death* may occur by heart paralysis, but more often by paralysis of the respiratory center. The symptoms may appear almost instantly, and are rarely delayed beyond an hour. In fatal poisoning death occurs usually in two to six hours. There are no constant *postmortem changes.*

Treatment.— The usual chemic antidotes. Emetics are not usually necessary. The symptomatic treatment should be mainly stimulating — ammonia, brandy, strychnin, attropin, warmth, and, when necessary, artificial respiration. The *chemic tests* for aconitin are of no value. The poison is best proved by its pharmacologic action on the frog's heart, by the sequence of quickening, slowing, quickening and slowing. (This is the more important since, in a legal case, a ptomain was isolated which gave the chemic tests for delphinin. The prickling is also very characteristic. Veratrin is the only other substance having a similar effect.) Aconitin is excreted mainly in the urine. It may be *absorbed* from the intact skin.

V. THERAPEUTICS.

The *collapse action* of aconitin is so strong that none of its other effects, except the local *anesthesia,* can be utilized. The former may, however, be useful, especially in short and *sthenic fevers,* as, for instance, in colds or acute rheumatism; it depresses here the overaction of the heart, and promotes sweating, and in both ways tends to lower the temperature. Very *small doses* should be employed for this purpose — 3 drops of the tincture for adults, repeated every hour until the pulse has returned to normal. It should be avoided, just as all other depressing agents, in long-continued fevers, such as typhoid.

Its *anesthetic action* has already been discussed under local anesthetics (p. 226), and it will also be considered under counterirritants (Chap. XXIX, E). It is used in the form of liniments (about 1 part of tincture to 10 of the liniment) and in 2% ointment of the alkaloid, mainly in neuralgias and rheumatism. It is given internally against trigeminal neuralgia.

The staphisagria is used in the form of ointment to destroy pediculi.

CARDIAC DEPRESSANTS.

Cardiac depressants may be defined as drugs which lower the activity of the heart. They may do so either by weakening the cardiac muscle or by stimulating the vagus mechanism. The former is done by large doses of almost any drug: the latter is alone useful therapeutically. A slowing of this kind may be valuable in regulating an overstimulated heart; but since it also produces a fall of blood pressure, it is particularly useful when a quick pulse is joined with a high pressure — as in sthenic fever. Quick pulse with low pressure indicates digitalis or strychnin, which act on the vasomotors as well.

The most useful Cardiac Depressants are: Aconite, Spartein, Veratrin, Colchicin, Potassium Nitrate.

VI. MATERIA MEDICA.

Aconitum (U. S. P.) [**Aconiti Radix,** B. P.].— (*Aconite, Monk's-hood, Wolfsbane.*) The tuber of *Aconitum Napellus,* Ranunculaceæ. Collected in autumn. Europe, Asia, and northwestern North America. (Other species contain similar principles.) Frequently cultivated in gardens. All parts of the plant are poisonous.

Active Constituents: Aconitin (not less than 0.5% U. S. P.) and similar alkaloids; resin, fat, sugar.

Preparations (made with ¾ to ½ alcohol; become turbid if mixed with water, but this does not destroy their activity):

Fluidextractum Aconiti (U. S. P.).— 0.4% aconitin. *Dose:* 0.05 c. c. = 1 ♏, U. S. P.

Tinctura Aconiti (U. S. P.).— 0.045% aconitin, 10% of drug (formerly 35%!). *Dose:* 0.1 to 1 c. c. (2 to 15 ♏) (0.6 c. c. = 10 ♏, U. S. P.).

Tinctura Aconiti (B. P.).—5%. Three-fourths alcohol. *Dose:* 0.3 to 1 c. c. (5 to 15 minims).

Aconitina (U. S. P.).— $C_{34}H_{47}NO_{11}$ (crystalline); sol. 3200 water, 22 alc. *Dose:* 0.15 mg. = 1/400 gr. (U. S. P.). Maximal dose, 0.3 mg. Its internal use is not advisable.

Aconitina (B. P.).— $C_{33}H_{45}NO_{12}$ amorphous.

Unguentum Aconitinæ (B. P.).— 2%.

Staphisagria (U. S. P.) [**Staphisagriæ Semina,** B. P.].— (*Stavesacre, Larkspur.*) The seed of *Delphinium Staphisagria* (other parts of the plant and other species are also poisonous), Ranunculaceæ. Temperate zone.

Constituents: Delphinin and similar alkaloids; fixed oil, mucilage.

Dose: 0.065 Gm. = 1 gr. (U. S. P.).

Preparations:

Unguentum Staphisagriæ (B. P.).— 10%. Used a parasiticide.

Fluidextractum Staphisagriæ (U. S. P.).— One-half alcohol. *Dose:* 2 c. c. = 30 ♏ (U. S. P.).

(B) VERATRIN GROUP.

I. MEMBERS, ETC.

The various species of veratrum contain at least ten closely related alkaloids. The **commercial veratrin** is a mixture of alkaloids obtained from the seeds of **cevadilla** (Asagræa officinalis, U. S. P.; Liliaceæ; synonym, Schoenocaulon officinale, B. P.). Mexico to Venezuela. Veratrum sabadilla is sometimes substituted. The principal constituent of this mixture, and the bearer of its physiologic actions, is **cevadin,** $C_{32}H_{49}NO_9$. It also contains the *veratrin of Wright* and *cevadillin* (the physiological action of these has not been investigated); and *sabadin* and *sabadinin* (weak actions).

White Hellebore (Veratrum Album, Liliaceæ) contains as its main active alkaloid **protoveratrin,** $C_{32}H_{51}NO_{11}$; this differs entirely in its actions from cevadin: the contractions of muscle are shortened, the height being increased, but fatigue occurring more readily. It seems to have a special action on nerve, prolonging the negative variation. It is very toxic. Veratrum also contains *jervin* (weakly active), rubijervin and pseudojervin (inactive), protoveratridin and probably others. White hellebore is not used in medicine, but is employed mainly as an insecticide on plants.

Study Materia Medica, Lesson 26.

Green Hellebore (Veratrum Viride) contains cevadin, jervin, pseudojervin, rubijervin, veratrin, and veratralbin. Its actions agree essentially with those of cevadin.

Black Hellebore, Helleborus niger, is in no way related to the above veratrum species. Its active principle, Helleborein, belongs to the Digitalis group.

Zygadenus (Death Camas), Liliaceæ, a poison plant of Western stock-ranges, owes its toxicity to veratrin bases, closely related to or identical with cevadin. (It contains at least sabadin, sabadinin and veratralbin; Slade, 1905).

The following description of the actions of Veratrin refer to the commercial alkaloid, *i. e.,* to cevadin. These actions agree in most respects with those of aconitin; but veratrin shows in addition a peculiar effect on striped and cardiac muscle, prolonging its contraction and tonus.

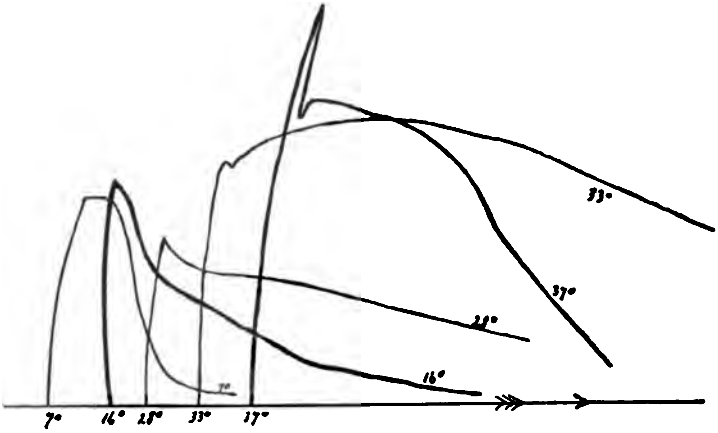

Fig. 68.— Effect of temperature on veratrin curve; gastrocnemius, frog. ⅔ natural size.

II. DETAILS OF ACTION.

1. Striped Muscle.[1]— When an animal, and especially a frog, has been poisoned with veratrin, it shows very striking peculiarities in its movements. It can contract its muscles with ordinary quickness, but it cannot recover its former position for some little time. The cause of this can be demonstrated on isolated muscle-nerve preparations (Figs. 68 to 71). It will be seen in these that the ascent of the muscle curve is as abrupt as usual, but that the relaxation is enormously prolonged. The muscle remains in what appears to be complete tetanus. It can be readily shown, however, that the phenomenon consists in a sustained single contraction.

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[1] Exercise 45.

If the nerve of a normal muscle-nerve preparation is laid on the veratrin muscle, a single shock sent into the latter causes a single twitch of the normal muscle, and not a tetanus as would be the case if the veratrin muscle were really tetanized.

The muscle is able to sustain a considerable weight throughout its contraction; the prolongation of the curve is therefore not due to a mere loss of elasticity, but is an active process. This is also shown by the fact that the formation of heat and the use of material is increased. The tension, the height and quickness of contraction, the irritability, the lifting and sustaining power of the muscle are all raised by veratrin, so that we must look upon its action as an increase of functional activity. It also lessens the effects of fatigue.

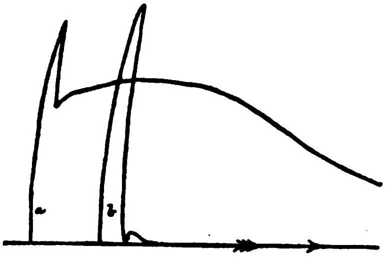

Fig. 69.—Effect of fatigue on veratrin curve: *a*, normal veratrin tracing; *b*, after partial fatigue; ½ natural size.

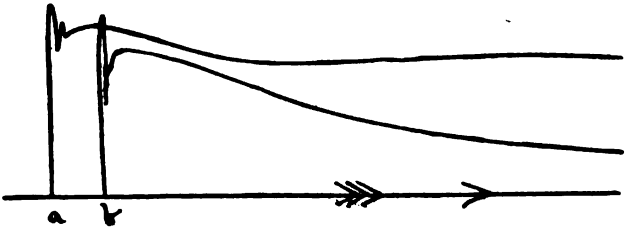

Fig. 70.— Effect of potassium (*b*), on veratrin curve (*a*), natural size.

The effect of veratrin is enhanced by agencies which stimulate the muscle, such as moderate heat (Fig. 68).

It is diminished by depression of the muscle, produced by cold or excessive heat (Fig. 68); by fatigue (Fig. 69); or by muscular depressants, such as potassium (Fig. 70) or ether.

(If the veratrin action is weak, cold increases the contracture, probably by adding its own contracture to that of the veratrin.) The action of veratrin is exerted directly on the muscle-cells; for it is more marked if the electrodes are placed directly on the muscle, and it occurs equally well after curare. Large doses of veratrin, indeed, paralyze the **motor endings,** without previous stimulation.

The application of veratrin to a muscle causes a slowly developing contracture, even in the absence of extraneous stimulation. Large doses paralyze all forms of muscle completely.

Whilst the muscular action of veratrin can be studied to best advantage on frogs, it occurs equally on *mammals*. In the latter, the contraction is not quite smooth, but often shows two to four elevations. This is due to variations in the excitability of the muscle-fiber at different times. The muscles of frogs poisoned with *glycerin* respond to single stimuli by prolonged contraction, the curve having a superficial resemblance to that of veratrin, but being rather more irregular. The glycerin contraction is, however, a true tetanus, due to greater irritability of the muscle substance; the action-current of each contraction sufficing to start another contraction. The phenomenon occurs also after curarization (Santesson, 1903).

Bottazzi's Explanation of the Veratrin-Phenomenon.—The prolonged contracture which is so characteristic of veratrin, is by no means confined to this alkaloid, but is also produced by Digitalin, Helleborein, Muscarin, Strychnin, etc., by cold, and by very strong electric stimulation. This *wide occurrence* signifies that the phenomenon is of fundamental physiologic importance. These measures also prolong the contraction of *cardiac and smooth muscle*.

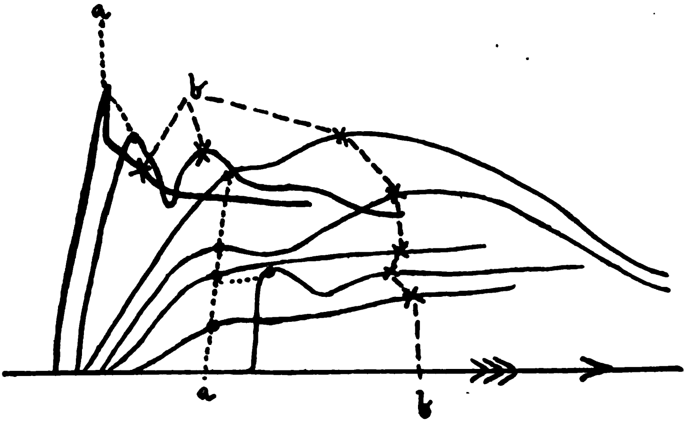

FIG. 71.—Normal veratrin curves, showing primary (*a*....) and secondary (*b* – – – –) contractions. Gastrocnemii of different frogs, air temperature, natural size.

A careful inspection of veratrin-curves generally reveals two contractions (Fig. 71): a primary contraction (a), which occurs with the normal rapidity, but is somewhat higher than normal, and which tends to relax quickly; and a secondary contraction (b), which occurs more slowly and lasts longer. The two contractions are more or less fused. This and other facts have suggested to Bottazzi (1901) the following plausible theory: Muscle cells contain two contractile elements, the fibrillary substance and the sarcoplasm. The former predominates in skeletal muscle, the latter in smooth muscle; cardiac muscle occupying an intermediary position. The fibrillary substance is by far the more excitable, so that it is alone stimulated in ordinary stimulation of skeletal muscle. Its contraction and relaxation are both quick, producing the normal muscle tracing, and the part (a) of the veratrin curve. The sarcoplasm can only be excited by very strong stimuli, or when it has been rendered abnormally sensitive. It has a longer latent period, and its contraction, and particularly its relaxation, are more leisurely. Its curve resembles that of smooth muscle, of which it forms the main element. Bottazzi assumes that the effect of veratrin and the allied drugs consists mainly in increasing the excitability of this sarcoplasm; and slightly that of the fibrillary substance; the main part of the veratrin curve, the secondary contraction (b), representing the contraction of the sarcoplasm. The effect of these drugs will therefore be proportional to the quantity of sarcoplasm: They act strongest on smooth muscle, next on cardiac, least on skeletal; as to the latter, they act more strongly on red muscles than on pale, on toad than on frog; on cold-blooded animals than on mammals; the sarcoplasm always predominating in the muscle which is more affected. The diversity in the form of the veratrin curves can be readily explained by this theory. The more the excitability of the sarcoplasm is increased, the more the two contractions will tend to fuse, and (b) overtop (a). If the contractility of the fibrillary substance is raised, as by heat, the two curves become more sharply separated (Fig. 68).

2. Cardiac Muscle.— The action is very similar to that on skeletal muscle, consisting in a quickened contraction and prolonged relaxation. The *frog's heart* shows the same phenomena as with digitalis: the ventricle is slowed, with systolic tendency, irregular and peristaltic contractions, systolic standstill. The auricle is much less affected.

The isolated mammalian heart (Hedbom-Langendorff) shows a primary slowing from stimulation of the peripheral vagus mechanism; then irregularity, and finally paralysis of the cardiac muscle, precisely as with digitalis.

3. Circulation in Intact Animals.— The effects of veratrin have the closest resemblance to those of aconite. They are mainly central. Therapeutic doses slow the pulse considerably, through central vagus stimulation. The blood pressure falls, although the vasomotor center is somewhat stimulated. Larger doses paralyze the vagus mechanism, so that the heart is quickened; but the pressure does not rise, the vasomotor center being also depressed. Very large doses quicken the heart even after atropin, indicating a direct stimulation of the muscle. The other **central effects** (on respiration, etc.) agree practically with aconitin (Fig. 72). In rabbits and guinea-pigs it causes a peculiar form of (medullary?) convulsions, consisting in "bucking" jumps.[1]

4. The **sensory nerve endings** also show the aconitin action, and even more strongly than with the latter drug. Sneezing and coughing are prominent symptoms. The prickling

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[1] Exercise 39.

and smarting are followed by *anethesia.* Protoveratrin causes the anesthesia without the preceding irritation, and thus resembles cocain.

5. Veratria produces **vomiting and diarrhea,** for the most part probably reflexly by acting on the sensory nerve endings. It may also corrode the gastric mucosa.[2]

III. TOXICOLOGY.

Poisoning by veratrin is not common. It presents the following **symptoms,** which are also charactersitic of aconitin: Burning in mouth, spreading to stomach; increased salivation, vomiting, diarrhea, abdominal pain; anxiety, headache, giddiness; pupils dilated; pulse slow and feeble; weakness, twitchings in muscles. Death by respiratory and circulatory collapse. Consciousness preserved till the end. Postmortem not characteristic.

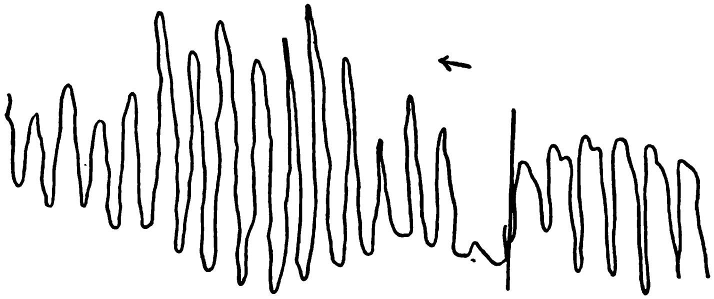

Fig. 72.—Veratrum viride on respiration, rabbit (lever method). Upstroke is inspiration.

In *non-fatal doses,* the symptoms are very slow in disappearing, and a double case of *slow poisoning* by continued small doses is on record: The two patients became very weak and thin, suffered from bloody diarrhea, insomnia, disturbance of the intellect, and delirium.

The **treatment** is the same as in aconite-poisoning (see p. 321). As the veratrin is rapidly excreted through the urine, it is well to administer hot tea as a diuretic.

IV. THERAPEUTICS.

It has been used after the manner of aconite, to secure the reduction of temperature by artificial *collapse.* It has no advantages. Its *local irritant* and anesthetic properties have caused it to be used in neuralgia, etc. The oleate is best adapted to this purpose.

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[2] Exercise 32.

V. MATERIA MEDICA.

Veratrum (U. S. P.).— Rhizome and roots of *Veratrum viride* (American Hellebore) or *Veratrum Album* (White Hellebore), Liliaceæ. North America.

Fluidextractum Veratri (U. S. P.).— Alcohol. *Dose:* 0.1 c. c. = 1½ ♏ (U. S. P.).

Tinctura Veratri (U. S. P.).— 10% (*formerly* 40%!); alcohol. *Dose:* 0.5 to 2 c. c. (7 to 30 ♏) (1 c. c. = 15 ♏, U. S. P.).

Veratrina (U. S. P., B. P.) — A mixture of the alkaloids (usually obtained from plants other than veratrum, especially Asagræa officinalis, U. S. P.). Soluble in 1750 water, 2.2 alcohol. *Dose:* 2 mg. = $^1/_{30}$ gr. (U. S. P.). The internal administration is not advisable.

Oleatum Veratrinæ (U. S. P.).— 2%.

Unguentum Veratrinæ (U. S. P.).— 4%.

Unguentum Veratrinæ (B. P.).— 2%.

(C) COLCHICIN.

This and another very similar alkaloid, colchicein, constitute the active principles of colchicum. The drug has some theoretic interest; and a toxicologic importance in the countries where it is indigenous. It is now rarely used in therapeutics.

Colchicin differs in certain characters from ordinary alkaloids, but its constitution is almost unknown.

Its action on mammals does not appear for a considerable time, even after intravenous injection, and it has almost no action on frogs. The reason for this is, that it is not the colchicin itself which produces the symptoms, but an oxidation product — oxy-di-colchicin — which is formed from it in the mammalian organism,— even by circulating it through excised organs,— but does not seem to be capable of formation in the frog's. Once formed, whether in the above manner or artificially by the action of ozone, it is toxic to frogs also.

The actions on the *sensory endings* and on the *heart* are similar to those of aconite and veratrin; the action on the *central nervous system* is almost purely depressant. This is in part secondary to the effect upon the *abdominal organs*. Colchicum causes extremely violent and quite uncontrollable vomiting and diarrhea (Exercise 43).

Postmortem, the mucosa of the intestine, especially the large, is intensely congested and often ecchymotic. Jacobj (1890) ascribes the intestinal effects to an increased irritability of the intestinal tract, so that the normal impulses, which ordinarily keep up a moderate peristalsis, now produce an extremely violent one. Other pharmacologists, however, assume a direct irritation.

TOXICOLOGY.

The **symptoms** of colchicum-poisoning do not appear for some time. Once they set in, they cannot be controlled; colchicum is therefore one of the most fatal of poisons. The symptoms refer primarily to the digestive tract: burning pains in abdomen, extremely violent vomiting and diarrhea, stools often bloody. For the rest, they are those of collapse, consciousness not being affected. *Death* occurs by failure of respiration. The *postmortem* appearances are not characteristic. There may, as has been said, be appearances of injury to the intestines from the strong peristalsis.

The **treatment** of poisoning, besides the usual alkaloidal antidotes, must be symptomatic.

THERAPEUTICS.

It will be seen that the pharmacologic actions of colchicum furnish no guide to its rational therapeutic application. It has been widely used on empirical grounds against *gout and rheumatism.* There is but little evidence of any superiority over aconite or purgatives, and its uncertain toxicity renders it so dangerous that its use should be unhesitatingly condemned. (However, authorities disagree very much on this point.)

MATERIA MEDICA.

Colchici Cormus (U. S. P., B. P.).— The corm of *Colchicum autumnale* (Meadow Saffron), Liliaceæ, Europe. Colchicin (at least 0.35%, U. S. P.); starch, gum, resin, fat, etc. The colchicin is contained in all parts of the plant.

Preparations:

Extractum Colchici Cormi (U. S. P.).— Made with acetic acid; pilular; 1.4% colchicin. *Dose:* 0.065 Gm. = 1 gr., U. S. P.

Extract Colch. (B. P.).— Made from the fresh corm. *Dose:* As the preceding.

Vinum Colchici (B. P.).— 20%. *Dose:* 0.3 to 2 c. c. (5 to 30 ♏).

Colchici Semen (U. S. P., B. P.).— At least 0.55% colchicin, U. S. P.

Preparations:

Fluidextractum Colchici Seminis (U. S. P.).— Two-thirds alcohol; 0.5% colchicin. *Dose:* 0.2 c. c. = 3 ♏ (U. S. P.).

Tinctura Colch. Sem. (U. S. P.).— 10% [B. P., 20%]; ⅔ alcohol; 0.05% colchicin. *Dose:* 2 c. c. = 30 ♏ (U. S. P.).

Vin. Colch. Sem. (U. S. P.).— 10%. *Dose:* As the preceding.

Colchicina (U. S. P.).—$C_{22}H_{25}NO_6$. Sol. 22 water, very sol. in alc. *Dose:* 0.5 mg. = $^1/_{128}$ gr. (U. S. P.).

Study Materia Medica, Lesson 26.

CHAPTER XVI.

QUININ GROUP.

THIS group contains certain of the cinchona alkaloids, especially quinin. The others, amongst which cinchonin and cinchonidin are the most important, are rather more convulsant; but they have not so far been sufficiently studied.

The group differs from those preceding in having a very marked *toxic action upon unspecialized protoplasm,* an action which exists to some extent in probably most of the alkaloids, but is generally obscured by their selective action on muscle and nerve. The phenomena which are noted with quinin are those of slowly dying tissues generally; an increased functional activity, followed by a diminution or cessation of function. On the whole, the paralyzing action is with quinin the most conspicuous and the most important. Large doses may produce paralysis directly, without preceding stimulation.

I. SUMMARY OF ACTIONS.

1. A toxic action upon all protoplasm, and an inhibition of ferment action.
2. A specific toxicity to the malaria organisms.
3. A diminution of heat-production in fever by direct action on the heat-producing foci.
4. A depressing action on the central nervous system, preceded by an obscure stimulation.

II. DETAILS OF ACTIONS.

1. General Toxicity.— The toxic action on protoplasm may be seen on lower organisms and isolated cells of all kinds. It acts most strongly on *cells possessed of ameboid and similar movement:* on infusoria, white blood-cells, ciliated epithelium, spermatozoa, insectivorous plants, muscle, etc.

A solution of 0.5 to 1 in 1000 is sufficient to inhibit the movements of *leucocytes* on the warmed slide, and a somewhat larger dose causes their disintegration. It acts in this manner also in the intact organism of the frog (Fig. 73). When the mesentery of this animal is exposed, leucocytes in active motion are seen inside and outside of the vessel (Fig. 73, *a*). If quinin is now applied, the movement of the cells outside of the blood will be arrested, whilst those in the blood stream still emigrate. The result is an accumulation of cells about the vessel wall (Fig. 73 *b*). If the quinin is injected into the vessel, the reverse takes place. The movement of the cells in the blood is arrested, preventing emigration, whilst those outside do not come into contact with the poison, continue to move away, and leave a clear zone about the vessel (*c*). This action does not occur in mammals, since the necessary dose would kill the animal. It is stated, however, that quinin diminishes the number of leucocytes in the blood. These, and most of the other actions of quinin, are shared by other alkaloids and bitter principles, but in much less degree.

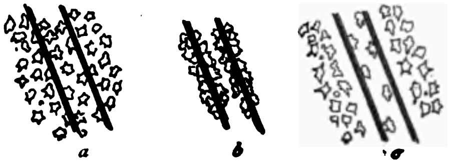

FIG. 73.—Diagram to illustrate the action of quinin on leucocytes, modified from Binz ("Das Wesen der Chininwirkung," Berlin, 1868). The thick lines represent the walls of the blood vessel, and numerous leucocytes are shown both inside of it and outside, distributed through the adjoining tissues. *a* represents the vessel before, and *b* after, the *local* application of quinin. *c* represents the effect of quinin injected into the circulation or lymphsac.

2. A much weaker, but none the less certain, action is seen on **yeast and bacteria.** The solution must contain 2 to 8 in 1000.

3. Striped Muscle.— The strength of the individual contractions may be increased as much as six times by moderate doses, but the muscle is much more quickly fatigued, so that the total work is less than in the unpoisoned muscle. As the same phenomenon is observed in curarized muscle, it must depend upon a direct action on the muscle-fibers. Somewhat stronger doses lower the contraction from the start (Fig. 74). Strong solutions produce a rigor after the manner of caffein[1] (Santesson, 1892).

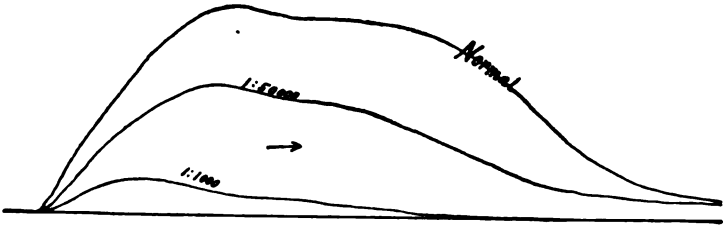

FIG. 74.—Quinin on muscular contraction.

4. The **cardiac muscle** in the frog is slowed by 1 : 50,000 solution and weakened in its contraction; its effectiveness is consequently diminished. The slowing occurs after atropin, and is therefore muscular. A 1 : 5000 solution kills the heart in a few minutes.

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[1] Exercise 45.

5. Mammalian Circulation.— In mammals and man small doses cause first a *quickened pulse* with *rise of blood pressure.*

The cause of the former is still under dispute, but is perhaps central. The rise of pressure depends mainly upon a *vasoconstriction,* but the cause of this is also still undetermined. It may possibly be due to a direct stimulation of the unstriped muscles of the blood-vessels.

Larger doses (in man, from 1 Gm. upward) cause a fall of blood pressure and slowing and weakening of the heart from the outset.

The fall is due in part to *vasodilatation.* The slowing and weakening of the heart are analogous to those observed in the frog. It is seen in the *excised* organ (Langendorff method). In this it often causes irregularity, but may regulate the heart if it is already irregular.

6. Smooth Muscle.— This shows no marked reaction to quinin.

But this is not saying that quinin does not act upon it, for a slight action on smooth muscle is *not easily accessible to observation.* It is certainly not very strong; the most likely example would be its action on the arterioles. *Contractions of the spleen, uterus, and intestines,* which may sometimes be seen, have been referred to such a direct action on smooth muscle, but this explanation is not very probable, since these phenomena are observed in only a very small percentage of cases; and as these contractions are never followed by paralysis, this would be opposed to all the other actions of the drug. No explanation can be given.

7. Another manifestation of the toxic action of quinin is in the **local irritation** which it produces at the place where it is applied. When given hypodermically it gives rise to severe pain, and may lead to *abscess formation.* When given by the stomach it causes in large doses *gastralgia, nausea,* vomiting, and diarrhea. It also retards the *absorption* of salts, and probably of food. Its excretion through the kidneys may give rise, with large doses, to *albuminuria and hemoglobinuria.*[1] And it seems not unlikely that a *skin eruption* which is sometimes observed, results from the irritant effects of its excretion through this channel.

8. The action of **unformed ferments** is retarded by it. Evidences of this antiferment action may be seen in many directions. The most important are: Diminution of the *oxygenating power of blood* and of protoplasm; slowed acidification of shed blood; lessening of the amount of hippuric acid formed when benzoic acid is circulated through the excised kidney. The various digestive ferments are hindered, but not to the same degree. It also lessens the glycogenetic function of the liver; *i. e.,* the postmortem transformation of the glycogen into sugar (Hoffmann, 1877).

9. Effects upon Digestion.— These can easily be deduced from the above data: It hinders the action of the ferments and absorption of the digested products. A favorable action which it might be supposed to possess as a bitter is largely counterbalanced by the unfavorable actions mentioned; consequently the utilization of food tends to be lessened when even small doses are used continuously.

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[1] The hemoglobinuria of malaria is often attributable to the quinin used in the treatment.

10. **Effects upon Metabolism.**—An influence upon this belongs to the earliest actions, and may be obtained even with doses too small to show any other effect.

From its toxic action on protoplasm one would expect to find first an increase and then a lasting diminution of metabolism, corresponding to the increase and diminution in functional activity.

This is indeed what is seen in regard to the excretion of *nitrogen*. There is first a slight increase, then a very marked diminution, which may reach as much as 39% with large doses. The ratio of urea to nitrogen is not altered by moderate doses (Prior, 1884).

One would be tempted to ascribe this diminution of nitrogen to the diminished utilization of food. Although this undoubtedly plays a part in it, the diminished excretion is out of all proportion, so that the nitrogen content of the body increases. Large doses of cinchonidin have a similar action.

This marked influence upon nitrogen metabolism is in conspicuous contrast to its want of influence upon *oxidation*. The quantity of O absorbed and CO_2 given off is practically unaffected by medicinal doses (up to 1.5 Gm.). There is a slight increase, but not more than can be accounted for by the excitement, chilliness, etc. The abnormally high gaseous metabolism of fever is reduced to normal by quinin; but this is probably the result of the antipyretic effect (Strassburg, 1874).

These effects upon metabolism are of great importance in explaining the effects upon temperature, as will be seen. But before taking up this subject, it is necessary to study the effects upon the central nervous system.

11. The effects upon the **central nervous system** consist in a rather *slow general paralysis,* probably preceded by stimulation; the latter is rather difficult to make out in mammals.

In *frogs* there is first an increased reflex irritability. This is followed by loss of spontaneous movement, then paralysis of respiration, and lastly of the cord, the phenomena bearing a general resemblance to those of the action of morphin (see p. 182).

The stage of stimulation is said to be more marked with cinchonin and cinchonidin, since these produce convulsions.[1] These are epileptiform in character, but their seat has not yet been definitely located. Probably they are not confined to any one center. In other respects these alkaloids agree qualitatively with quinin.

The depressing effects upon the hemispheres are much less marked in *mammals,* but a *diminished appreciation of pain* can be distinctly made out, and upon it rests the employment of quinin against neuralgic and rheumatic pains.

One of the most constant early symptoms of larger doses of quinin is headache, ringing in the ears, and disturbed vision, a complex of symptoms grouped together under the name of *cinchonism.* These are not due to any action on the central nervous system, but to *local changes.*

The auditory and visual phenomena have generally been referred to local circulatory changes: The retina is said to be anemic, whilst the internal ear is congested, postmortem (Kirchner). Wittmaak (1903) claims that this congestion is not due to quinin, but to death, and points out that changes of blood pressure do not produce deafness. On the other hand, he demonstrates changes in the cells of the spiral ganglion, by the Nissl stain. He is therefore inclined to attribute the auditory effect to a specific toxicity of quinin to these cells. The same origin is assigned by Altland, 1904, to the visual changes, the retinal cells being altered. Cinchonism is very subject to *idiosyncrasy,* being much more easily produced in some individuals.

With still *larger doses,* there are *photophobia, deafness,* and *blindness,* at first partial, later complete. These are probably partly central. There are *difficulty of speech, confusion of ideas, somnolence.* Then *loss of consciousness,* alternating with *delirium, coma,* and at times *convulsions.*

It has been doubted whether the latter are really due to quinin or to the accidental presence of some of the convulsant cinchona alkaloids.

General paresis may appear, preceded by general depression and muscular weakness. The final symptoms are those of *collapse,* due to general paralysis of the central nervous system, and in part also of the heart. The *respiratory center* shows a short primary stimulation with following more marked paralysis. The latter is the usual *cause of death.* But since the medullary centers are not markedly affected until very late, quite large doses are often survived. The *fatal dose* is usually given as 8 Gm., but 30 Gm. have been recovered from.

It is doubtful, however, how much of this really entered the circulation, since the sulphate is very insoluble, so that a large amount may not have been absorbed.

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[1] The samples (Schuchardt's) examined by the author had, however, very little convulsant action; the cinchonin had more than the cinchonidin.

The *peripheral nerves* are not markedly affected, except the poison be applied directly, when it will kill them just as other protoplasm.

12. Effects on Temperature.— *When the temperature is normal,* small doses of quinin cause a slight rise. In somewhat larger doses, but not sufficient to cause a marked collapse, it gives an insignificant fall. In doses which produce collapse it causes, of course, a marked fall of temperature through this condition — *i. e.,* by lowering the circulation and the respiratory exchange.

In hyperpyrexia the temperature is markedly lowered even by moderate doses. This antipyretic action is not as pronounced as with the antipyrin and salicylic acid groups.

The *cause of this reduction* of febrile temperature appears to be quite complicated, but it consists mainly in a *diminished heat production through a direct action on the heat-producing foci.* It could conceivably result from one or more of the following:

Diminished Heat Production:	Increased Heat Loss:
Direct action on heat-producing foci.	Direct action on vasodilator mechanism of skin.

Indirect action on heat production and dissipation through thermoregulating centers.

General collapse action.

Calorimetric experiments show that the heat production is considerably diminished, whilst the heat loss is not greatly increased. Consequently quinin acts mainly upon *heat production.*

Quinin produces a slight *dilatation of the cutaneous* vessels, which, since the general blood pressure is not diminished by ordinary doses, increases the heat loss. But since this occurs also with normal animals whose temperature is not markedly affected by quinin, it cannot play a very important rôle.

Quinin lowers the temperature in animals in which the *spinal cord* has been divided. Consequently, its action is mainly *peripheral,* although any collapse which it may produce would also express itself in a fall of temperature.

The evidence so far, then, indicates that *the action is a local one upon the heat-producing foci;* and this is indeed what one would have expected *a priori.*

The most important seat of heat production is in the muscles; next, in the glands. We have already seen that quinin at first increases and then diminishes muscular work, and it is not unreasonable to suppose that it would have the same effect upon the production of heat in these organs. And it will be remembered that the heat production of the body is, in accordance with this explanation, at first increased, then diminished by it. There is less direct evidence in regard to its action on glands and other body-cells; but when the general depressing effect upon all cells is remembered, and, further, its interference with ferment actions, inside and outside of the cell-body — actions which play so large a part in metabolic processes — it seems very reasonable that the general metabolism, and in consequence the production of heat, should be lessened by it in cells other than those of the muscle.

We find a direct evidence of its effects upon metabolism in the excretion of nitrogen, since this is at first slightly increased, but later largely diminished. But here a difficulty arises. We have been accustomed to look upon the excretion of CO_2 as an index of chemic changes resulting in the liberation of energy and consequently of heat; and the excretion of CO_2 is not affected by quinin. But since the calorimeter shows conclusively that the production of heat *is* diminished by it in fever, this interesting fact merely forces us to the conclusion that oxidation is *not* the only source of heat; that heat may also be liberated by other changes — by the splitting or hydration of nitrogenous molecules, in the course of which the nitrogen is converted into urea; and that these changes are those which are hindered by quinin. If it be supposed that this form of heat production is especially prominent in fever,— and this seems quite probable,— the fact that quinin acts on febrile, and not on normal, temperature is also explained.

13. Action on Malaria.— The specific action of quinin in this disease is due to its toxic effects upon the protameba causing the disorder.

This organism is especially susceptible to it. On a slide a 1 : 10,000 solution immediately arrests the movements of the parasite, and similar phenomena occur in the body. About three hours after the administration of quinin by the mouth, the endoglobular forms of tertian and quartan fever become immobile, granular, lose their nucleoli and their affinity for certain stains. Several hours later they may be seen deformed and fragmented (Lo Monaco and Panichi, 1899).

The *other cinchona alkaloids* have a similar, but much weaker, action on the protozoa.

The quinin does not act equally on the parasite in all the stages of its development. Its strongest action is upon the forms which are just breaking into spores (Fig. 75, 10), and upon the free-swimming organisms (11); it is much weaker upon the older segmenting bodies (7 to 9), and least upon the young endoglobular forms (1 to 6).

Since the latter exist in the blood just before the paroxysm, and their sporulation gives rise to the characteristic chill and fever, and since quinin does not act upon them, it will not be effectual against the oncoming paroxysm. But if it is given at this time it will be present in the blood when the spores are liberated, and as these are most susceptible to its action, it will kill them and thus prevent the development of the new cycle (providing that the dose has been sufficiently large). It should therefore be given several hours before the expected paroxysm so as to allow time for its absorption. The dose should then be quite large: 1 to 2 Gm. given two to three hours before the expected attack (which will in all probability occur), or 0.3 Gm. four to five times a day in the interval; 0.5 Gm. per day should be continued for several days after the last chill. It also seems to act as a prophylactic. It must be taken continuously for this purpose, since it is quite rapidly excreted — 0.1 to 0.2 Gm. every morning.

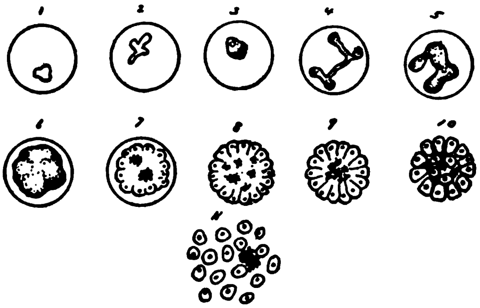


FIG. 75.—Some of the principal forms assumed by the plasmodium of tertian fever in the course of its cycle of development (after Thayer and Hewetson).

III. OTHER THERAPEUTIC USES OF QUININ.

1. Fevers.— The antipyretic effect of quinin may be used in any fever, *e. g.,* typhoid; but the coal-tar antipyretics have largely forced quinin out of this field. It possesses an advantage over these in a more prolonged action and in less risk of collapse; but it does not take effect as rapidly, and the large dose required — 0.3 to 1 Gm.— produce the annoying cinchonism. This can be greatly lessened by giving it with a bromid. Another unpleasant side-action seen in a few individuals consists in a *scarlatinal dermatitis or urticaria.* It is said that this is abolished by atropin. Like the other antipyretics, it is most efficient when the temperature has a natural tendency to fall. It takes about two hours to act, and should, therefore, be given about that time before an expected fall of temperature.

It has been suggested that its efficiency in fever is due to an antiseptic action on the blood. This is not the case, since bacteria are very resistant to it, and would not be affected by it in the concentration in which it could exist in the blood.

2. **Splenic Enlargement.**—With the spleen of malaria its effect is, of course, largely indirect; but good results have been claimed for it in other cases. If this be true, they could perhaps be connected with its action in diminishing the number of leucocytes.

3. **Neuralgias and headaches** are sometimes benefited by its use. The cause of this action is still obscure. It may be due to its general analgesic action. Another theory which has been suggested is, that these neuralgias, etc., are due to the presence of nitrogenous waste-products, and that quinin acts by limiting the formation of these.

4. **Colds** are frequently treated by it, in doses of from 0.06 to 0.2 Gm. (1 to 3 grs.). When it has any effect at all, this must depend upon its anodyne and antipyretic actions.

5. **As a bitter** substance it may act as a stomachic and consequently as a tonic; but it is rather inferior to other bitters, since its continued use leads to an impairment of digestion and of absorption.

6. **Locally,** the sulphate has been used as dusting powder in ulcers, as antiseptic, styptic and stimulant.

IV. METHODS OF ADMINISTRATION.

The administration presents some little difficulty, since on the one hand certain of its salts are very little soluble, and the others have a very bitter taste.

Small doses of quinin sulphate or hydrochlorid may be easily given in the forms of pills or capsules; or in solution, the taste being disguised by glycyrrhiza. (No acid must be prescribed with the latter!) The tannate or the pure alkaloid may also be given, but they are probably less efficient. Being insoluble, they are practically tasteless, and act only as they enter into combination with the acid of the gastric juice.

Large doses of quinin sulphate in pills or powder are probably largely wasted, since they are not dissolved or absorbed; the sulphate requires 720 parts of water for solution. The hydrochlorid is more soluble (1 : 18) but the bisulphate is the best (1 : 8.5).

It is customary not to prescribe the bisulphate directly, but the sulphate brought into solution by the addition of a sufficient quantity of dilute sulphuric acid. The quantity of acid should be rather in excess. If it is only just sufficient, some sulphate will be precipitated on the tongue by the alkaline saliva, and give rise to a very persistent after taste. There will be very little of this if an excess of acid is used and the mouth rinsed afterward.

The ordinary quinin salts are not well adapted for *hypodermic use* on account of their irritant action. They produce pain, indurated nodules, and sometimes abscess formation. The hydrochlorid has the property of forming peculiar soluble and non-irritant compounds with a number of substances. Three parts mixed with two of antipyrin was formerly used. Recently a compound formed by mixing 1 Gm. of the hydrochlorid, 0.5 Gm. of urethane, and 2 c.c. of water has been warmly recommended. The quinin is liberated from this compound in the body. The hypodermic injections have the advantage of securing a quicker action. They are made deep into the gluteal muscles. This compound can also be used intravenously; but the possibility of a cardiac action enjoins great caution (Gaglio, 1903).

V. ABSORPTION, FATE AND EXCRETION.

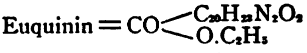
Quinin is fairly readily absorbed from the stomach, and excreted promptly by the urine. The excretion begins within half an hour after taking and continues fairly rapidly, but traces may be found for several days. Other secretions may also contain it. It is ordinarily stated that the greater part of the quinin is excreted unchanged; but in the dog 86 to 88% are completely oxidized (Merkel, 1902). In the blood, the quinin is said to occur mainly within the red corpuscles.

VI. SUBSTITUTES FOR QUININ.

The disadvantages of quinin — the bitter taste, cinchonism, skin eruptions, digestive derangement, idiosyncrasy, etc.— make an efficient substitute for the alkaloid very desirable. As far as the antipyretc effect is concerned, quinin may, indeed, be entirely displaced by the coal-tar antipyretics, but these are for the most part inefficient against malaria. For this action the modification must be introduced into the quinin itself. The *tannate* obviates some of the disadvantages, since it is insoluble until it reaches the intestine, when the quinin is slowly liberated. But it lacks promptness and certainty of action. A more useful product is obtained by converting the alkaloid into an ester, as in

Euquinin (Quinin-ethyl-carbonic ester).

Quinin $= H.C_{20}H_{23}N_2O_2$



$$\text{Euquinin} = CO\begin{cases}C_{20}H_{23}N_2O_2\\O.C_2H_5\end{cases}$$

This product is stated to have exactly the same action as quinin, and in the *same doses*, but to be free from its disadvantages. It is almost insoluble in water, and therefore practically tasteless and free from irritant actions. The quinin is liberated in the alimentary canal by the decomposition of the euquinin, but this occurs so slowly that there is no cinchonism. The decomposition takes place more steadily and more certainly than in the case of the tannate.

Aristochin (neutral carbonic-ester of quinin) and *Saliquinin* (salicylic ester) have similar properties and uses. It may be introduced into the phenetidin molecule, yielding a product (*Chinaphenin*) which combines the qualities of quinin and phenacetin — without special advantage.

VII. MATERIA MEDICA.

Cinchona (U. S. P., B. P.).—*Peruvian Bark.*—The bark of various species of *Cinchona* (Rubiaceæ). They must contain at least 5% of total alkaloids, and at lea.. 4% of anhydrous ether-soluble alkaloids (U. S. P.).

Cinchona Rubra (U. S. P., B. P.).—The bark of *C. succirubra.*

The trees yielding cinchona are indigenous to the mountainous districts of the Andes in South America, at a height of 3,400 to 1,200 meters. Trees growing below this level contain but little alkaloid. The natives were acquainted with the medicinal value of this "tree of health," and the bark was brought to Europe by the early explorers. It received its name, cinchona, from the Countess Chinchon, who was one of the first Europeans to receive its benefits.

At present practically all the barks of commerce are from cultivated trees, the original forests having been largely depleted. This cinchona cultivation is carried on in a number of subtropical mountainous countries possessing a rather moist climate — especially in India.

The U. S. Pharmacopœia does not discriminate between the different species. Between thirty and thirty-six of these are recognized; but many are probably mere variations and hybrids, and a recent author has attempted to reduce the species to four.. The most important are: C. Calisaya (yellow bark); succirubra (red bark); officinalis; lancifolia; micrantha; scrobiculata.

The alkaloidal content of the different barks varies greatly. It has been considerably increased by cultivation, some samples yielding to 13% of quinin. The alkaloids are contained in all parts of the plant, in the parenchymal cells. The root bark contains the most, then comes the ordinary bark.

The *constituents* are: Certain acids (quinic, quinovic, etc.); *Tannin,* as cinchotannic acid (2 to 4%), which yields green color with iron; cinchona red, a derivative of the preceding (both are glucosids); gum, wax, resin, etc.

A very large number of alkaloids have been isolated; many of these undoubtedly arise in the course of the manipulations. The most important are in italics:

Quinin,[1] *Quinidin,* Quinicin.
Quinamin, Conquinamin, Quinamidin, Quinamicin.
Cinchonin, Cinchonidin, Cinchonicin, Homocinchonicin.

(Those on a line are isomeric.)

When the crystallizable alkaloids have been separated from cinchona extracts, evaporation of the mother liquor yields a brown extract, *Chinoidin* (Quinoidin), which contains amorphous alkaloids, mainly Di-cinchonicin and Di-quinidin.

* *Cuprea Bark,* from Remija pedunculata, Rubiaceæ, contains for the most part the same alkaloids, but no cinchonidin. It is used in the manufacture of quinin.

Preparations.—These have no advantage over quinin, and since they are incompatible with iron, and the alcoholic preparations also with water, the alkaloid should be preferred.

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[1] Name from *quina,* bark.

Fluidextractum Cinchonæ (U. S. P.) [*Ext. Cinch. Liq.*, B. P.]; 4/5 alcohol, with glycerin; 4% alkaloids. *Dose:* 1 c. c. = 15 ♏ (U. S. P.).

Tinct. Cinchon. (U. S. P., B. P.).— 3/4 alcohol, with glycerin; 20% = 0.75% alk. *Dose:* 4 c. c. = 1ʒ (U. S. P.).

Infusum Cinchonæ Acidum (B. P.).— 5%. Contains a small proportion of aromatic sulphuric acid. *Dose:* 30 c. c. = 1 oz.

Tinctura Cinchonæ Composita (U. S. P., B. P.).— 10% of Red Cinchona; Bitter Orange, Serpentaria. *Dose:* 2 to 10 c. c. (½ to 2 drachms).

The above preparations contain glycerin and 66 to 80% of alcohol.

* *Tinctura Cinchonæ Detannata,* N. F.— The official tincture with the tannin removed by iron.

* *Elixir Cinchonæ* and *Elixir Cinchonæ Detannatum,* N. F., contain 3% of Cinchona. *Dose:* ad libitum.

* *Elixir Quininæ Compositum,* N. F.—(A substitute for cinchona.) 0.2 quinin sulphate, 0.1 cinchonidin s.; 0.1 cinchonin s.; in 100 c. c. Aromatic Elixir.

Alkaloids and their Salts.— Their *dose* is 0.03 to 1.5 Gm. (½ to 25 grs.) [0.03 to 0.05 as tonic; 0.05 to 0.25 for colds; 1.0 in malaria] (0.25 Gm. = 4 gr., U. S. P.).

	1 part is soluble in	
	water	alcohol
Quinina: $C_{20}H_{24}N_2O_2 + 3H_2O$	1550.	0.6
Quininæ Bisulphas: $Qu.H_2SO_4 + 7H_2O$	8.5	18.
" Hydrobromidum: $Qu.HBr + H_2O$	40.	0.67
" *Hydrochloridum:* $Qu.HCl + 2H_2O$	18.	0.6
" Salicylas: $2Qu.C_7H_6O_3 + H_2O$	77.	11.
" *Sulphas:* $Qu._2H_2SO_4 + 7H_2O$	720.	86.
Cinchonidinæ Sulphas: $C_{19}H_{22}N_2O)_2.H_2SO_4 + 3H_2O$	63.	72.
Cinchoninæ Sulphas: $(C_{19}H_{22}N_2O)_2.H_2SO_4 + 2H_2O$	58.	10.

Preparations:

Oleatum Quininæ (U. S. P.).— 25%

Elixir / *Glyceritum* } *Ferri, Quininæ et Strychninæ Phosphatum* (U. S. P.).— (See Index.)

The N. F. *Elixirs:*

* Elixir Quininæ Compositum; Elixir Quininæ et Phosphatum Compositum; El. Cinchonæ et Ferri; El. Cinch., Ferri, Bismuth, et Strych.; El. Cinch., Ferri, et Bismuth; El. Cinch., Ferri et Calcii Lactophosphatis; El. Cinch., Ferri, et Pepsini; El. Cinchonæ, Ferri, et Strychn.; El. Cinchonæ, Pepsini, et Strych. *All contain 0.4% of cinchona alkaloids.* (Teaspoonful = 0.016.) *Dose:* 4 to 8 c. c.

A favorite way of giving quinin for malaria in India is in the form of *Warburg's Tincture* — * *Tinctura Antiperiodica,* N. F. This contains 2% of Quinin Sulphate (each tablespoonful = 0.3 Gm.) and carminatives (rhubarb, aloes, camphor, and aromatic drugs) which probably aid in the absorption of the quinin.

Warburg's Pills.—* *Pilulæ Antiperiodicæ,* N. F., contain the same ingredients in solid form. (The pill form is quite irrational.) Each pill = 4 c. c. of the tincture.

Synthetic Products:

* *Euquinin* (Quinin Carbonic Ester).— White, light, fleecy powder of crystalline needles. At first tasteless, then a faint bitter taste. Almost insoluble in water, soluble in alcohol and fat solvents. Decom-

posed by acids. Administered in powder, pills, or suspended in milk, in the same dose as quinin; should be given earlier before the expected attack.

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* Unofficial.

**Salochinin* (Quinin Salicyl Ester) resembles the above, but also develops the action of salicylates.

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* Not official.

CHAPTER XVII.

SERIES OF COAL-TAR DERIVATIVES.

The former high price of quinin caused chemists and pharmacologists to look about for cheaper efficient substitutes. It was attempted to make quinin or similar substances synthetically, departing from quinolin, one of the decomposition products of quinin. Whilst this search did not result in an artificial quinin, nor even of any substance analogous to it in action, it brought to light a very large number of substances, in some respects even more valuable than the alkaloid itself, and served to direct attention to the pharmacologic significance of the derivatives of the aromatic series, or, as they are more commonly called, of coal-tar.

It was found that all the simpler compounds built up from the benzol nucleus (with a very few exceptions) possess certain physiologic actions in common, as follows:

Summary of Common Actions of Coal-tar Derivatives:

Central Actions: 1. Stimulation, followed by more pronounced *depression* of the entire central nervous system, but particularly:

2. An *antipyretic* action on the heat-centers, and

3. An *analgesic* action in neuralgias.

Local Actions: 4. A *coagulant,* irritant and toxic effect on all forms of proteid and protoplasm — on tissue cells, bacteria, and ferments.

5. A quinin action on all forms of muscle.

6. Local anesthesia.

7. The formation of methemoglobin.

The actions are exerted in a different manner and to a different degree by the several members of the series, mainly in two directions, so that two groups can be made out.

(*A*) *Antipyretic Group.*— This is distinguished by the predominance of the action on the heat-regulating center.

(*B*) *Antiseptic Group,* characterized by a much more marked local action on protoplasm, which determines the usefulness of the members as antiseptics. The effect upon the thermic center passes much more readily into general collapse than with the former group.

Relation to Quinin.— It will be seen that the action of the series agrees in a general manner with that of quinin, the principal difference lying in the degree in which the different actions are exerted. In the antipyretic group the principal effect is upon the heat-regulating center; in the antiseptic group it is upon the protoplasm, and is so violent that it produces necrosis locally and collapse centrally. Quinin has both these actions in a less pronounced degree, producing its main effects by a mild paralyzing action on protoplasm. On the other hand, none of the coal-tar products possesses the specific anti-malarial power of quinin.

(A) ANTIPYRETIC GROUP.

This comprises all those coal-tar products in which the antipyretic action is therapeutically the most important. Those which are used mainly as antiseptics but which also possess antipyretic properties (such as guaiacol or the salicylates) will be considered under the antiseptic group.

The antipyretics can be arranged in five chemic groups, which are, with their most typical members: (1) Pyrazol derivatives: *Antipyrin;* (2) Anilin derivatives: *Acetanilid;* (3) Phenetidin derivatives: *Phenacetin;* (4) Phenylhydrazin derivatives: *Antithermin;* (5) Quinolin derivatives: *Thallin, Quinalgen.* (The chemistry of these compounds is discussed later.)

I. DETAILS OF ACTIONS.[1]

1. Action on Temperature.[2]— The effect upon the *normal temperature* is slight, just as in the case of quinin, and may result in a small rise, unless with doses sufficiently large to produce a marked collapse action; but *febrile temperature* is in most cases reduced to normal, or even below, by even moderate doses.

This occurs, whatever the cause of the hyperpyrexia — whether bacterial infection, heat puncture, cocain, excessive exercise, hot baths, etc.

Mechanism of the Antipyretic Action.— This has been investigated mainly on rabbits rendered hyperpyretic by puncture of the corpus striatum. *Calorimetric experiments* show that the reduction of temperature is accomplished mainly by *increased heat-loss.* This might occur through an increased production of sweat, or by exposing a larger amount of blood to the cooling influence of the surroundings by *dilatation of the cutaneous vessels.* In the case of this group it is accomplished mainly by the latter means.

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[1] Unless otherwise stated, the description applies to all the members of the series.

[2] Exercise 36.

The dilatation can be plainly shown by the plethysmograph. And since the reduction occurs even after atropin, which suppresses the secretion of sweat, the latter is not essential. The *vasodilatation is confined to the cutaneous vessels,* and this is important, since, if the blood-vessels in the remainder of the body were also dilated, the circulation through the skin would be diminished rather than increased. This limitation of the vasodilatation to the region concerned with the regulation of temperature also points to the central action.

There is also some diminution of the heat production by limitation of the *metabolism.* When the temperature of an animal is *normal,* the members of this group have no very constant or marked effect upon nitrogenous metabolism. Acetanilid increases the excretion of *nitrogen;* larger doses of antipyrin (2 or 3 Gms.) cause a small but unmistakable decrease in both gaseous exchange and nitrogen excretion. In *fever,* however, all the coal-tar antipyretics produce a marked decrease of gaseous and nitrogen metabolism; but this comes on *after* the fall in temperature has set in, and must be regarded as an effect, and not a cause, of this fall. The metabolism is always abnormally high in hyperpyrexia, and removal of the latter brings with it a decrease in the former.

Antipyrin and the other drugs of this group act, then, upon the heat-regulating center when the temperature is abnormally high, and cause its reduction to or near normal. by increasing the heat loss.

This action must be conceived as a restoration of the centers to their normal pitch. Numerous facts go to show that in fever, as well as in health, the center exerts a regulating influence; but the temperature which it strives to maintain is an abnormal one.

There is a peculiar difference in the susceptibility of *different fevers* to antipyretic drugs: High continuous fevers react least, those of an intermittent type being most amenable; and with these, again, the greatest effect is produced when the action falls into the period of the natural decline of temperature.

Sometimes antipyretics may even produce a " paradoxical action "— a rise in temperature.

2. The action on the remainder of the **central nervous system** consists in stimulation, followed by paralysis. We can distinguish a narcotic, a convulsant, and a collapse effect, these passing insensibly into each other.

(A) A slight **narcosis** — a diminished sensibility to pain and perhaps a very slight degree of somnolence — may be seen with all antipyretics, and enhances their usefulness.

This analgesic effect is most pronounced in *neuralgia and headache*. It is produced by all members of the group, as also by salicylates, quinin, etc. Unlike the analgesia produced by morphin, it is not effective in other forms of pain. The mechanism of this action has not received any satisfactory explanation, but it seems likely that it rests on a vasomotor action on the intracranial (meningial) circulation (Wiechowski, 1902).

Acetanilid, antipyrin, and phenacetin have proved beneficial in *diabetes insipidus;* according to a number of clinical observers (*e. g.*, Hirschfeld, 1904). The mechanism of this action is quite obscure.

(B) After the narcosis, and before the depression of the remainder of the central nervous system, come the **convulsant effects.**

The seat of these convulsions is probably diffuse, but they appear to start first in the brain. They are intermittent in character, and are preceded by increased reflex irritability. They are rarely seen with the antipyretics.

(C) Following this there is *unconsciousness,* **collapse,** and, finally, total *paralysis*. The *pulse* is first accelerated, then slowed. The *respiration* becomes dyspneic and then diminished. There are sometimes vomiting and dilatation of the pupils. The skin is cyanotic and covered with cold sweat.

This collapse action is strongest in the mother substances — anilin, quinolin, phenetidin, phenylhydrazin, and carbolic acid, and generally in the members of the antiseptic group; so strong, indeed, that the action of these cannot be controlled, and they are hence unfit for internal administration.

Of the more usual antipyretics, acetanilid produces probably the strongest collapse effects; then come antipyrin, phenacetin, and lactophenin, in the order given.[1]

This collapse — produced by large doses of the drugs themselves — must not be confounded with a collapse sometimes appearing after small doses in fever, and due, not to the drugs, but to the reduction of the temperature. We deal in these cases with a collapse which really pre-existed, but which was *masked by the hyperpyrexia*. An elevation of temperature produces effects in certain ways antagonistic to those of collapse, and may hide this condition. On removing the stimulus of the high temperature, the hidden collapse will of course become apparent. It would do so not only after the administration of antipyretic drugs, but also if the temperature were reduced by cold baths or any other means.

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[1] Notwithstanding its slight solubility, acetanilid has even been absorbed from wounds in sufficient amount to produce toxic symptoms.

3. The **peripheral actions** of the antipyretics are comparatively weak.

(A) They may produce some *local irritation* of the stomach, resulting in vomiting; but this action is much less pronounced than in the case of quinin. Even those members which are almost insoluble possess a sharp warm taste.

(B) The **antiseptic action** of the antipyretics is not very strong. They are, however, sometimes used as antiseptic, astringent, and *hemostatic dusting powders* (acetanilid; or antipyrin in 5% sterilized solution). They are less poisonous and less irritating than iodoform.

(C) All drugs of the coal-tar series act more or less upon the blood, inside of the body, producing **methemoglobin,** and in larger doses causing a disintegration of the corpuscles. This action is much more pronounced in the mother-substances — anilin, phenylhydrazin, etc. — and in the antiseptic group. It leads to a peculiar cyanosis, and contributes to the collapse. It is peculiar of this group that the methemoglobin formation proceeds much more weakly in shed blood than it does in the body.[1] The usual antipyretics may be grouped, as regards this action, in the following manner:

1. Medium doses merely render the oxygen of the Oxyhemoglobin less labile: Antipyrin and Phenacetin and their derivatives.
2. Medium doses cause the formation of methemoglobin inside of the corpuscles, without destroying these: Thallin, Kairin, Exalgin.
3. Medium doses are apt to cause methemoglobinemia with destruction of the corpuscles: Acetanilid, Benzanilid, Formanilid, Pyrodin, Chrysarobin, Pyrogallol.

(D) **Striped muscle** shows a somewhat increased efficiency on direct stimulation, and a weak curare action.

(E) **The heart** is first accelerated, and later slowed. This is due to direct action upon the heart muscle. The *vasomotor center* is not affected by moderate doses (with the exception of the part controlling the cutaneous vessels through the thermal centers). In consequence, the *blood pressure* depends solely upon the cardiac action, being at first increased and later diminished. In doses producing collapse there is paralysis of the vasomotor system, and consequent fall of blood pressure.

4. **Side-actions.**—The reduction of temperature by these antipyretics is apt to be accompanied by certain side-actions which may become dangerous if the dose be too large, or

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[1] Exercise 21.

if the person be especially predisposed to them. They vary quantitatively to a considerable extent in different individuals, and even with the same person at different times. They may be referred for the most part to the central nervous system, the most frequent being *excessive sweating, chills, cyanosis, skin eruptions, digestive disturbances, symptoms resembling cinchonism, and collapse.*

The *sweating* is due to the increased circulation through the skin, and is produced in the same manner, and has the same significance, as the critical sweat of fever. It must be looked upon as beneficial rather than otherwise, since it aids the reduction of temperature. But should it become too troublesome, it can be suppressed by small doses of atropin.

The cutaneous hyperemia is perhaps also responsible for the *skin eruptions.* They are particularly frequent after antipyrin.

The tendency to this eruption, as also to a *stomatitis* which is often seen, increases with the repeated use of the drug.

Phenylhydrazin produce very similar local actions on the skin (eczema erythematosum and papulosum) and on the alimentary canal (gastroenteritis).

The *chills* occur when the temperature begins to rise again, and are due to a diminished circulation through the skin, just as the chills of malaria. They are not, therefore, to be attributed to the drugs, but are rather a sign that the action of the antipyretic has worn off.

Gastric symptoms are due to local irritation, but are not frequent. *Cinchonism* symptoms are very rare, but have been reported. The *cyanosis* is due to the methemoglobinemia.

The *collapse* is the most dangerous complication. As has been said, this is usually due to the fall of temperature, and where there is reason for supposing the existence of such a masked collapse, when the fever is of a markedly asthenic type, great caution should be used in reducing the temperature, whether by drugs or by any other means. The production of collapse is most frequent in menstruating women. The cause of this is not understood.

It has often been stated that the antipyretics paralyze the *heart.* This is more than doubtful with ordinary doses. The belief probably resulted from the moderate slowing which is always produced, partly as a direct effect upon the heart muscle, but mainly as the result of the lowered temperature.

Renal irritation, varying from slight diuresis without histologic change, to violent, desquamative, hemorrhagic, parenchymatous nephritis, may be produced by all coal-tar derivatives. There is not, however, any danger of nephritic lesions from ordinary doses of the antipyretics. Thallin produces a peculiar papillary nephritis.

Chronic Poisoning.—The continued use of acetanilid ("'headache-powders") has occasionally caused the development of a drug habit, with craving and withdrawal symptoms. An individual predisposition appears to be necessary, for the condition is relatively rare; but it should be guarded against in the administration of the drug. The symptoms of chronic acetanilid poisoning consist in methemoglobinemia (chocolate-colored blood) with the histologic blood changes of pernicious anemia; marked leucocytosis. Cyanosis; cardiac weakness; progressive mental and physical debility. Methemoglobin may also appear in the urine. (D. D. Stewart, 1905.)

5. Dosage and Choice.— On account of the possibility of a direct collapse action if the *dose* is relatively large, the antipyretics must be administered with care.

In general, it may be said that, from the smallest effective dose (0.2 Gm. for acetanilid, 0.5 to 0.7 Gm. for antipyrin or phenacetin), the extent of the antipyretic action increases with the dose of the drug, until the normal temperature has been reached. Up to this point there is practically no danger of a direct collapse action. But if the dose necessary to secure this result be exceeded, the toxic effects will set in.

The average antipyretic dose may be stated as 0.5 Gm. (7 grains) of acetanilid; 0.8 Gm. (10 grains) of phenacetin; 1.2 Gm. (20 grains) of antipyrin. In beginning the treatment, this dose has to be repeated once or twice, with an hour's interval, until the normal is reached. After this, the single dose is repeated whenever the temperature begins to rise. Four or five doses are required per day to keep the patient practically fever-free. The action does not persist after the drug is excreted, and consequently the administration must be continuous, in the manner indicated. Those antipyretics which are rapidly excreted (as is phenocoll) are therefore less useful.

In regard to details, and in determining the *choice of the particular substance* to be used, experience is the best guide. The same holds here as in other cases: Very much more can be accomplished by any one drug that is thoroughly understood by the user, than can be done with a number of drugs with which he has had only limited experience.

6. Absorption and Excretion.— The coal-tar antipyretics are rapidly absorbed and excreted. They are for the most part decomposed in the body, but the benzol ring is not attacked. The derivatives are excreted as paired compounds with sulphuric and glycuronic acid (see below). The oxidation products often give a smoky color to the urine; this may also be tinged with methemoglobin. Ferric chlorid colors the urine red after antipyrin, reddish brown after acetanilid. The active anilin and phenetidin derivatives (acetanilid, phenacetin, etc.) are oxidized to paramidophenol ($C_6H_4.NH_2.OH$), which is excreted mainly as a paired compound. The urine gives the indophenol reaction.[1]

The **treatment of poisoning** by overdoses of the antipyretics is the same as for collapse from other causes — stimulants, heat, etc. (see Aconite).

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[1] Exercise 13.

II. THERAPEUTIC USES.

We have already touched upon their slight *narcotic* and *local antiseptic action.* Their principal use is in the reduction of fever temperature. The entire therapeutics of fever may be summarized in this place.

Therapeutics of Fever.— The treatment of fever has always been tinctured by the views which have successively prevailed concerning its nature. When fever was considered mainly as a subjective condition, attention was directed principally to the sensations of heat and thirst, and there arose the class of *refrigerants,* including the dilute mineral acids (see Chapter XXVI, B). They are useful even now, especially carbonated drinks, in conjunction with other treatment. Since the alkalinity of blood is diminished in fever, the organic acids are also useful in this connection, since they tend to make the blood more alkaline.

As physical observation came more into fashion, the quickened pulse of fever fixed the attention of the clinicians, and it was attempted to combat all the conditions of fever by slowing the pulse. The so-called class of *cardiac depressants* came into vogue. They include substances acting in various ways:

Aconite and *veratrin,* producing vagus stimulation and general fall of blood pressure. *Digitalis,* producing a slowed heart, but heightened blood pressure. *Nauseants,* as tartar emetic, acting secondarily through the nausea. *Potassium* salts, which have a direct action on the heart.

It does not need great acumen to perceive that remedies with actions so diverse could not be successful if employed indiscriminately in all cases of fever. Some have still a place in rational therapeutics, but only when used for special indications: *Aconite* offers advantages over the antipyretics if the fever is of a short high type; *digitalis,* if the heart is very irregular. Whether *nauseants* and *potassium* are ever indicated against fever, as such, is very doubtful.

When the thermometer was introduced into medicine, and it was recognized that an elevation of temperature was the best index to febrile conditions, *antipyretic measures* came into prominence.

The theoretically possible ways in which drugs may reduce temperature have been discussed previously. Practically, they are reduced to the following:

1. Lowering of the constant of the thermo-regulating center (coal-tar antipyretics).
2. Lowering of heat production by action on foci (quinin).
3. Dilatation of cutaneous vessels (with consequent diaphoresis) (aconite, nauseants, diaphoretics, alcohol).
4. Collapse action (aconite, veratrin).

To these could be added:

5. Removal of heat by mechanical means (cold baths, effusions, or pack).

Methods 2, 3, and 4 are discussed elsewhere.

In regard to the application of antipyretic measures in fever, it is essential to bear in mind that they have *no direct effects on fever, except upon the temperature.*

Exceptions to this general statement are the actions of quinin in malaria, of salicylates in acute articular rheumatism, of cinnamic acid in tuberculosis, and the analgesic action of the coal-tar products.

For the rest, they strike neither at the cause of the fever nor at any symptoms other than those resulting from the hyperpyrexia. They make the type of the disease neither less severe nor shorter.

In malaria, *e. g.*, antipyretics may prevent the development of a paroxysm of fever; but they do not attack the cause of the disease as does quinin; for their effect is not lasting, nor does their continued administration lead to a reduction in the size of the spleen.

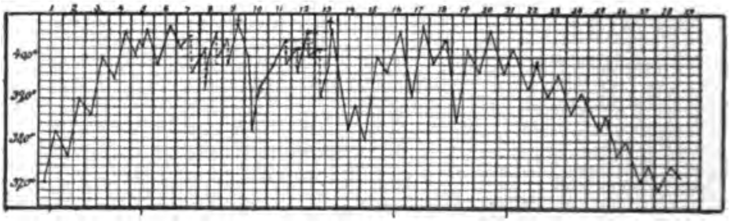
They are a symptomatic and not a specific mode of treatment. And symptomatic treatment must always be carried on with great care, lest more harm than good should result. But where it is not possible to attack the cause, it is often advisable to remove objectionable symptoms. The question then is, *May a reduction of fever temperature be useful?* It must be borne in mind that hyperpyrexia is often a protective mechanism. This is shown by the onset of collapse in certain cases, if the stimulus of the high temperature be removed. Also, bacteriologic research has shown that with most bacteria the optimum temperature for development is confined within very narrow limits, which are exceeded by the temperature of fever. The *tendency* of fever may perhaps be said to be useful in all cases, but as a matter of fact it usually leads to more damage than good. The cells of the mammalian organism are not adjusted to work under the conditions of so high a temperature. It is detrimental to them as well as to the bacteria, and sometimes more so. Its effects (for a fuller description see first edition, pages 391 to 395) consist in lassitude and enervation, in general discomfort, restlessness, irritability, and delirium. The respiration and heart are quickened. The metabolism, and especially the elimination of nitrogen, is greatly increased. This leads to emaciation, diminished alkalinity of blood, degeneration of important organs, etc. All these, joined perhaps to a deleterious action of the increased metabolic waste-products, produce a condition highly detrimental to the patient. These conditions, in so far as they have not already passed into permanent anatomic changes, are promptly and totally removed by restoring the normal temperature. Measures for this purpose are therefore indicated whenever these symptoms arising from hyperpyrexia become very pronounced, and unless there are special contraindications. They should not be used, for instance, if there is ground for suspecting a masked collapse. Nor are they of any use in high continued fevers.

Antipyretic measures of this kind are mainly cold baths and the coal-tar antipyretics, and these have their respective drawbacks and advantages. The chief advantage of cold baths lies in the fact that there is no danger of a direct collapse action; but there is no need for this danger with antipyretics if their dose be properly adjusted. The latter save the patient the exertion, discomfort, and shock of a cold bath. As, in the case of baths, the temperature-regulating mechanism is not adjusted to normal, the patient experiences all the ordinary effects of an attempt to reduce the temperature below normal: chills, cyanosis, etc.; and the metabolism is increased rather than diminished. The action of the chemic antipyretics is also more pronounced and lasting (Fig. 76), and their analgesic action is of marked value in influencing the subjective condition of the patient. In regard to this *narcotic action*, antipyrin and acetanilid are about on a level; they are surpassed by phenacetin. This action is especially useful when the fever is associated with delirium.

The objections to cold baths are very greatly lessened if *tepid baths* are used. These are not so much antipyretic as stimulant, improving the blood pressure, digestion, and sleep. They increase the nitrogen excretion. It has been shown that cold baths cause a considerable rise of blood pressure in acute fever, whereas camphor, caffein, strophanthus, ether, or alcohol are generally ineffectual in this condition. As to the chemical antipyretics, the theory has been advanced that they interfere with the natural protective bodies of the serum. It has been shown, however, that this is not the case, at least as far as the agglutinin of typhoid serum is concerned. In conclusion, it may be said that *the best general treatment of fever consists in a combination of antipyretics and graduated baths.*

The use of the antipyretics in *neuralgia, headache and migraine* has been previously described. Acetanilid (in small doses) is most commonly used, and is quite efficient.

The addition of caffein appears to enhance the analgesic effect in many cases, and would indeed be useful when the drugs are used as antipyretics, to counteract the tendency to collapse, and the cardiac actions. The addition of salicylate and bromids is similarly useful.



Initial period. Fastigium. Amphibolic stage. Defervescence.

FIG. 76.— Antipyretics in typhoid fever. Dotted lines = cold baths; + = antipyretics (Strümpell).

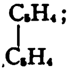
Sod. bicarb. or Ammon. Carb. are often added to increase the solubility. The official Pulv. Acetanilidi Comp. is representative of the *proprietary headache powders.* These contain from 50 to 70% of acetanilid (see Journ. Am. Med. Assoc., 1905, p. 791). Their indiscriminate use by the public is dangerous.

III. INFLUENCE OF THE STRUCTURE OF ANTIPYRETICS UPON THEIR ACTION.

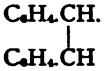
The enterprise of manufacturers of synthetic products has overwhelmed the profession with almost numberless antipyretics; but it must be confessed at once that the number of really new and valuable products is comparatively small. The great mass of this material consists simply of insignificant variations in the established products, introduced for the purpose of evading patents; and amounts to little more than do the various flavorings in the elixirs of the older materia medica. It can only do harm by creating confusion, and should be abolished as speedily as possible. The selection of the worthy products from this collection would be an almost hopeless task, were it not that certain definite laws have been deduced from the experimental evidence, according to which we may foretell the action of a coal-tar derivative from its composition, with almost absolute certainty. In this way many new compounds can be adjudged as unworthy of extended trial. A presentation of some of these laws will therefore be of practical value, aside from their scientific interest.

The antipyretic action really resides in the benzol ring. Yet benzol (C_6H_6) itself is not antipyretic, because it cannot enter into reaction with the body cells; this capacity of reacting may be given to it by substituting for one of its [H] atoms an [OH] group, as in carbolic acid, C_6H_5OH; or still more strongly by an NH_2 group, as in anilin, $C_6H_5.NH_2$ (Phenylhydrazin, $C_6H_5NH.NH_2$ being yet stronger); or by both as in paramidophenol, $C_6H_4.OH.NH_2$.

In a few modifications of the benzol ring, the action is quite wanting; thus in Pyridin, C_5H_5N; in Naphthalin,

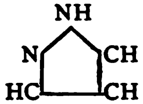


$\begin{array}{l}C_6H_4\\ |\\ C_6H_4\end{array}$; in Phenanthren,



$\begin{array}{l}C_6H_4.CH\\ \quad\;\; |\\ C_6H_4.CH\end{array}$. But it reappears in Quinolin,

$\begin{array}{l}C_6H_4\\ |\\ C_4H_3N\end{array}$, and is also present in the pyrazol ring,



We repeat that the power of acting is giving to the benzol or other chain, by replacing H through OH, or NH_2, or both. The substances so produced are the so-called "mother-substances." They are strongly antipyretic, but they also produce collapse. Before they can be used in practice, this collapse action must be diminished. This may be done by replacing the [H], either of the [OH] or of the [NH_2], by other radicles; the reduction of toxicity being greatest if the substitution is made in the NH_2.

These substituted compounds act only after the mother-substance is liberated from them in the body. Their action is therefore more gradual, less violent, and more easy of control.

The influence of the substituted radicle is as follows:

The reduction of toxicity is greatest if the substituted radicle is an alkyl ($CnH_2n + 1$ or $CO_2.CnH_2n + 1$); less if it is an acidyl ($CO.CnH_2n + 1$). If several H atoms are substituted, the toxicity will be less if both an acidyl and an alkyl radicle are introduced, than if both radicles be of the same kind.

The toxicity and the therapeutic qualities *both* diminish with the size of the introduced radicle. The most useful is the ethyl (C_2H_5) or acetyl (C_2H_3O) radicle; with the methyl or formyl group, the toxic action is too great; with larger groups, and particularly with aromatic groups, the compound becomes so resistant that the therapeutic action is reduced almost to nothing. This is true of the citrate and salicylate radicles. Such compounds are of course correspondingly harmless.

The above laws must be modified if the compound is decomposed in the stomach with liberation of the mother-substance. It must also be remembered that the radicles must be introduced into the ring by substitution; the mere addition of acid radicle, forming salts, does not modify the properties of the original substance. Therefore, Anilin Acetate ($C_6H_5.NH_2.HC_2H_3O_2$) preserves the original toxic action of anilin; whereas this is greatly weakened in Acetanilid ($C_6H_5.NH.C_2H_3O$).

The substitution of an H by I, Br, or Cl, does not modify the antipyretic or toxic action of the original substance.

IV. COMPOSITION, SPECIAL PROPERTIES, AND MATERIA MEDICA OF THE MORE IMPORTANT ANTIPYRETICS.

Before giving in detail the characters of the individual antipyretics, it may be well to recapitulate briefly the *points which will determine their value:*

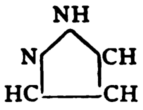
The ideal antipyretic must be reliable in securing a fall of febrile temperature. This fall must be prompt, but not too abrupt; it must be lasting; and when the effect passes off, the temperature must not rise too suddenly. The analgesic effect should be strong. The drug should not be decomposed in the stomach (or by 0.2% HCl). The toxic dose should be considerably higher than the therapeutic dose. In the latter, the drug must not of itself cause collapse conditions, nor methemoglobinemia, nor profuse sweating, nor skin eruptions. It should not have a bad taste, nor should it irritate the stomach. If it is to be used hypodermically, it must be soluble in water; otherwise great solubility is of no advantage.

Of the compounds which have been proposed so far, Para-acetphenetidin (Phenacetin) seems to fulfill these demands most satisfactorily.

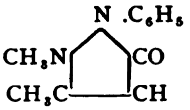
1. PYRAZOL DERIVATIVES.

The *doses* of these compounds agree with antipyrin.

Antipyrina (U. S. P.) [**Phenazonum,** B. P.].— Phenyldimethyl pyrazolon, Analgesin, Dimethyloxychinizin; $C_3HN_2O(CH_3)_2.C_6H_5$. Obtained by the condensation of phenyl hydrazin with aceto-acetic ether, and methylation of the product. It is a derivative of Pyrazol:



Pyrazol.



Antipyrin.

Antipyrin is a white powder, sol. in 39.5 water, 38.2 alc. It is quickly absorbed, but slowly excreted. *Dose:* 0.25 to 0.6 to 1.5 Gms. (4 to 10 to 25 grains), in solution; (0.25 Gm. = 4 gr., U. S. P.). (Incompatibilities, see p. 76.)

Antipyrin unites readily with acids to form *salts.* These have no advantage. Examples are:

Salipyrin (Antipyrin Salicylate) and *Tussol* (Antipyrin Amygdalate).

Substitution Products:

Iodopyrin is an iodin substitution product. It shows the properties of antipyrin, but does not improve upon them.

Pyramidon.— An [H] of [CH] in antipyrin is replaced by [$N(CH_3)_2$]. This compound is three times as active as antipyrin, its action lasts longer, and it is no more dangerous. *Dose:* 0.2 to 0.6 Gm. Especially recommended in the hectic fever of phthisis.

(*Anilipyrin* is a condensation product obtained by fusing one equivalent of acetanilid, and two of antipyrin. It dissolves readily in

Study Materia Medica Lesson 28.

water, and is less toxic than acetanilid, but possesses no advantage over mere mixtures of the two.)

Homologues:

Tolypyrin.—The C_6H_5 of Antipyrin is replaced by $C_6H_4.CH_3$. The resulting compound is as active as antipyrin, but more irritant. It resembles this also in its solubility and dose. Its salicylate is known as *Tolysal.*

2. ANILIN DERIVATIVES.

Acetanilidum (U. S. P., B. P.) (*Antifebrin,* Phenylacetamid).—$C_6H_5NH(CH_3CO)$.—Prepared by boiling anilin ($C_6H_5.NH_2$) with glacial acetic acid, replacing an [H] of the [NH_2] by the acetyl radicle [$COCH_3$]. A white powder or crystals, of a warm taste. Soluble in 179 parts of water, and in 2.5 parts of alcohol. *Dose:* to 0.5 Gm. (8 grs.) (0.25 Gm. = 4 grs., U. S. P.); daily dose, to 4 Gm.; in powders or capsules.

Anilin itself is an active antipyretic, but markedly toxic; acetanilid also acts as anilin, being decomposed into this substance. It has still considerable tendency to cyanosis and collapse. It is useful as an analgesic, in small doses, but should not be used in full doses. This holds yet more of its homologue, *formanilid* (C_6H_5NHCOH—replacement of $COCH_3$ of acetanilid by COH). *Exalgin* ($C_6H_5NCH_3CH_3CO$—replacement of H of NH in acetanilid by CH_3) is weaker. The higher homologues—*Benzanilid* ($C_6H_5NH.C_7H_5O$—$COCH_3$ replaced by C_7H_5O)—are practically inactive. In *Euphorin* (Phenylurethan) the $COCH_3$ of acetanilid is replaced by $CO.OC_2H_5$. The result is a compound combining the qualities of acetanilid and of urethane, but in no way superior to simple mixtures.

Acetanilid Mixtures:

Pulvis Acetanilidi Compositus (U. S. P.).—Acetanilid 70, Caffein 10, Sod. Bicarb. 20%. *Dose:* 0.5 Gm. = 7½ gr.

Similar mixtures are:

* *Migrainin* (Antipyrin 85, Caffein 9, Citric Acid 6%).

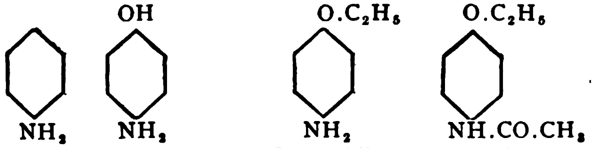
* *Hemicranin* (Phenacetin 5, Caffein 1, Citric Acid 1).

These are given in the same dose.

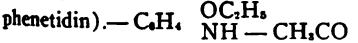
3. PHENETIDIN DERIVATIVES.

When it was noticed that the body renders anilin (or acetanilid) less toxic by oxidation to paramidophenol, the thought lay near to begin with the administration of this body, or, as it is still quite toxic, of its derivatives.

If the H of the OH is alone replaced, phenetidin results, which with its salts, is also too toxic. The product does not become useful until one of the H atoms in NH_2 is also substituted, as in phenacetin.



Anilin. Paramidophenol. Phenetidin. Phenacetin.



Acetphenetidinum (U. S. P.)[1] [**Phenacetinum,** B. P.] (Para-acetphenetidin).—$C_6H_4\begin{matrix}OC_2H_5\\NH-CH_3CO\end{matrix}$. The acetylization product of para-amidophenetol. A white crystalline powder, of a warm taste, soluble in 925 water; in 70 of boiling water; in 12 of alcohol. *Dose:* 0.3 to 0.6 to 1.0 Gm. (5 to 10 to 15 grains), as powder; (0.5 Gm. = 7½ gr., U. S. P.).

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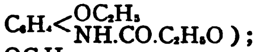
* Not official.

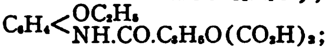
[1] See purity tests, Exercise 10.

Phenacetin presents as yet the best result in the attempt of lessening toxic effects and yet preserving therapeutic activity. However, it still possesses some toxicity, and this and its insolubility have encouraged the investigation of similar compounds. The substitution of the acetyl radicle ($CO.CH_3$) by the radicles of higher acids does indeed lessen the toxicity and increase the solubility and the analgesic action, but at the expense of antipyretic value. These compounds with higher acids are also subject to decomposition by the acidity of the gastric juice, resulting in the liberation of the toxic phenetidin. They are therefore incompatible with acids, and if used should be administered with sodium bicarbonate. Their dose is about the same as of phenacetin, or somewhat larger.

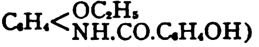
To this class belong:



Lactophenin (acetyl replaced by lactyl = $C_6H_4{<}\begin{matrix}OC_2H_5\\NH.CO.C_2H_5O\end{matrix}$);

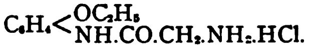


Apolysin (by citric acid radicle = $C_6H_4{<}\begin{matrix}OC_2H_5\\NH.CO.C_3H_5O(CO_2H)_2\end{matrix}$;



Phenosal (acetyl replaced by salicyl = $C_6H_4{<}\begin{matrix}OC_2H_5\\NH.CO.C_6H_4OH\end{matrix}$) is especially inactive.

More deserving is *Thermodin,* in which the H of the NH of Phenacetin is replaced by $CO_2C_2H_5$. This causes considerable loss of toxicity, without greatly impairing the therapeutic activity. A somewhat different compound is *Phenocoll;* in this the acetyl of phenacetin is replaced by glycocoll.



Phenocoll hydrochlorid: = $C_6H_4{<}\begin{matrix}OC_2H_5\\NH.CO.CH_2.NH_2.HCl.\end{matrix}$

White powder of a burning taste reminding of salicylates, which is greatly lessened by dilution. Soluble in 16 parts of water. Incompatible with alkalies. It is about equal to phenacetin in therapeutic and toxic action, being used in the same dose (but as solution). It differs from it in its great solubility, and consequent rapid but short action. It is especially suited for hypodermic injection (in ½ the oral dose). Specific effects have been claimed for it on malaria, but it does not affect the plasmodium any more than other coal-tar antipyretics. *Phenocoll acetate* is still more soluble (2 parts of water). *Phenocoll salicylate* (*Salocoll*) is much less soluble.

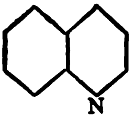
It was already mentioned that *Phenetidin* ($C_6H_4.OC_2H_5.NH_2$) and its salts are much too toxic for therapeutic use. Only one of these, the Citrate (*Citrophen*), has been placed upon the market, and this has fallen into a deserved neglect. In the compounds *Malakin* and *Malarin* the toxicity has been lessened by replacing the H_2 of the NH_2, in Malakin by the salicyl rest $CH.C_6H_4OH$; in Malarin by acetophenon $C{<}\begin{matrix}CH_3\\C_6H_5\end{matrix}$. The latter is still toxic. The former is rendered non-toxic, but also inactive, by the salicyl.

4. PHENYLHYDRAZIN DERIVATIVES.

Phenylhydrazin, $C_6H_5.NH.NH_2$, was one of the early starting-points in the invention of antipyretics. It is itself strongly antipyretic, but is the strongest blood poison of the antipyretic series. This toxicity is shared by its salts and simple substitution products. To these belong: *Hydracetin* (Pyrodin) (H of NH_2 replaced by acetyl;

$=C_6H_5.NH.NH.COCH_3$); *Antithermin* (H_2 of NH_2 deplaced by levulinic acid); *Orthin*. The dose is given as to 0.1 Gm.

5. QUINOLIN DERIVATIVES.

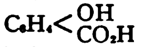
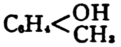


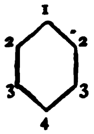
The fact that *Quinolin* — C_9H_7N — is one of the decomposition products of Quinin was the incentive to the investigation of the antipyretic action of the coal-tar products. The compounds so discovered have now only a historical interest; they are indeed antipyretic, but also very toxic (Thallin, $C_9H_6N.H_4.CH_3O$; Kairolin, $C_9H_7N.H_3.C_2H_5.H_2SO_4$; Kairin, $C_9H_6(OH)N.H_3.C_2H_5$). They fell into neglect, but the discovery of phenacetin stimulated the search of similar compounds of quinolin. Such is *Quinalgen* (Analgen), $C_9H_5(OC_2H_5)(NH.COC_6H_5)N$. This is safer than other quinolin derivatives, but becomes active only as the benzoyl-group is split off by the gastric juice. It is therefore of inconstant action. It is a white, almost insoluble powder. *Dose:* 0.5 to 1.0 Gm.

(B) ANTISEPTIC GROUP.

The second coal-tar group, that of the *antiseptics*, is characterized by the prominence of the toxic action on protoplasm when brought into direct contact, and of the collapse action when acting from the circulation.

I. MEMBERS — INFLUENCE OF STRUCTURE ON ACTION.

As was stated previously, benzol, C_6H_6, the mother substance of the coal-tar series, is itself practically inactive, because it cannot react with protoplasm. This capacity is given to it by replacing part of the H atoms by other groups, especially by OH (forming phenols) or by CO_2H (forming acids); or by both. This develops the peculiar antiseptic, toxic and irritant qualities of the coal-tar antiseptics. The OH radicle is the most active, the antiseptic and toxic actions increasing with the number of OH groups (*i. e.*, progressively from phenol C_6H_5OH, to resorcin, $C_6H_4(OH)_2$ and pyrogallol, $C_6H_3(OH)_3$). The introduction of the CO_2H group alone (*i. e.*, benzoic acid, $C_6H_5.CO_2H$) does not render the substance very active. The introduction of both OH and CO_2H in the ortho-position[1] (*i. e.*, salicylic acid,  $C_6H_4<{OH \atop CO_2H}$) results in a compound which is less toxic than phenol, but which has peculiar antiseptic properties. The antiseptic quality may also be brought out by other acidyl groups ($COCH_3$, etc.), the activity being proportional to the size of the introduced molecule. NO_2 also develops the antiseptic action, but adds its own toxicity to that of the phenols. The substitution of an H of the C_6H_5 in phenol by alkyls (cresols,  $C_6H_4<{OH \atop CH_3}$) leads to an increase of the antiseptic power, and diminishes at the same time the toxicity to



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[1] When the substitution occurs in the position 1.2, the ortho-compound results; 1:3 gives the meta-compound; and 1:4 the para-compound.

tissues. Higher homologues introduce no important modifications. The substitution of halogens increases the antiseptic action.

The group which gives the valuable antiseptic, but also the undesirable toxic and caustic, qualities to these compounds, is the OH.

The violence of its action may be moderated, as in the salicylic acid, or in the cresols; or it may be masked by replacing its H by other radicles. These esters (*e. g.*, salol, $C_6H_4.OH.CO_2C_6H_5$) will develop their action when decomposed into their phenol. Combinations which are so firm as to prevent this liberation (*e. g.*, the sulphocarbolates) are neither antiseptic nor toxic: in fact, it is by the formation of such compounds that the organism protects itself against these poisons.

The antiseptic and local actions of the salicylates or other salts are also much less than those of the corresponding acids.

The coal-tar antiseptics may be divided into the following groups: I. *Phenol, Salol;* II. *Cresols;* III. *Resorcin, Pyrocatechin, Hydrochinon, Arbutin, Pyrogallol;* IV. *Creosote* Derivatives; V. *Dyes;* VI. *Salicylic Acid;* VII. Other aromatic acids, Balsams; VIII. *Naphthalin, Naphthol* and Quinolin derivatives.

II. SUMMARY OF ACTIONS.

1. A coagulating action upon proteids, determining the death of cells with which they come in contact, and resulting in irritation and inflammatory changes.
2. An excitation, followed by more pronounced depression, of the central nervous system.
3. The formation of methemoglobin.

Historical.— In the form of the natural mixtures, the antiseptic properties of this group have long been known. The smoking of meat is certainly a very ancient practice; and one of the methods of embalming practised by the Egyptians utilized largely balsams and products rich in essential oils,— the latter being very closely related to the aromatic series. The isolated substances, however, belong to the achievements of the nineteenth century. Creosote was first made in 1832, carbolic acid in 1834, and it was almost thirty years later than this before they were used in surgery.

III. DETAILS OF ACTION.

I. Phenol.

Phenol (carbolic acid, C_6H_5OH) shows very typically the characteristic properties of the entire aromatic antiseptic group. It is also the most widely known and used of these antiseptics. It owes this high popularity to its being the pioneer of the group, through its introduction by Lister. This popularity is no longer justified, for we now possess other derivatives superior to it in every respect. However, it serves admirably to illustrate the main features of these antiseptics, and is therefore accorded the most prominent place.

1. Local Actions.— Most of the members of this group coagulate, and thus destroy the structure of proteids, and, in consequence, of protoplasm. This protoplasmic toxicity is particularly great in phenol, and accounts for its irritant and antiseptic action.[1]

When pure carbolic acid, or a strong solution of it, is applied to the skin or mucous membranes, it acts as a caustic. It produces burning and pain, then numbness and anesthesia, wrinkling and softening of the epidermis, the color of the skin becoming first white, then red, and finally brown. A dry scab forms, which separates without pus. Creosote has a similar but much weaker action. In weaker solutions neither is caustic, and they determine merely some wrinkling and blanching of the epidermis. But even a 5% solution of the acid may cause necrosis, especially when applied continuously to the extremities. This enjoins caution in the use of carbolic dressings. Ninety-five per cent. alcohol, glycerin and fats are antidotal to the local effects of carbolic acid. None of the other members of the group have such a marked caustic action, although salicylic acid effects a softening of the epidermis, which leads to its use in removing corns. It is important to note that its salts, the salicylates, have no caustic action, but are nevertheless antiseptic. All the members have, however, some local action, which finds its expression, with internal administration, in *nausea, vomiting, and diarrhea,* being similar to quinin in this way. The vomiting is also favored by the repulsive taste of some of these drugs. This local irritant action further shows itself after large doses at the place of excretion — *e. g.*, in *nephritis* with casts, albuminuria, and hemoglobinuria (Fig. 77). *Skin eruptions* which occur occasionally may be ascribed to this irritation and to the dilatation of the cutaneous vessels. Strong solutions brought into direct contact with a muscle, decrease its excitability. The coagulant action on proteids also determines the most characteristic property of the group, namely, their *antiseptic effects.*

This coagulation is a molecular, rather than a chemic, process. That is to say, phenol and the other drugs of the group do not enter into chemic combination with the proteids, but precipitate them by changing the character of the *medium,* somewhat after the manner of alcohol or neutral salts. A short action of this kind is sufficient to kill the protoplasm. But the coagulant substance itself, not being combined and used up in this process, is free to penetrate further, which is not the case with the metallic antiseptics. This penetration is also favored, in the case of carbolic acid, by its volatility, a factor which is absent with salicylic acid and most other members of the group. The metals enter into insoluble, permanent, chemic combination with the protoplasm, and this effectually prevents the further penetration of the antiseptic. This greater penetrating power of the antiseptics of the aromatic group is of considerable practical importance. Further, just as different proteids present different degrees of precipitability with alcohol, ether, and chloroform, or with the different neutral salts, so they are acted upon differently by the various members of this series; and this suggests the explanation of the fact that different bacteria present a very different degree of resistance to them; and that certain members may be almost specific in a disease — as salicylic acid in acute rheumatism — where the other members are of but very little use.

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[1] Exercises 15 to 18.

For this reason also, it does not follow by any means that the toxicity to the tissues must needs be proportional to the toxicity to bacteria. On the contrary, the usefulness of an antiseptic which is to be applied to the body, is determined by its combining a great toxicity to bacteria with a minimal action on tissue cells. The ideal antiseptic, in this respect, has not been found, and probably does not exist; but the cresols, guaiacol, etc., approach it much more closely than phenol or the metallic salts. (For the use of antiseptics, see below.)

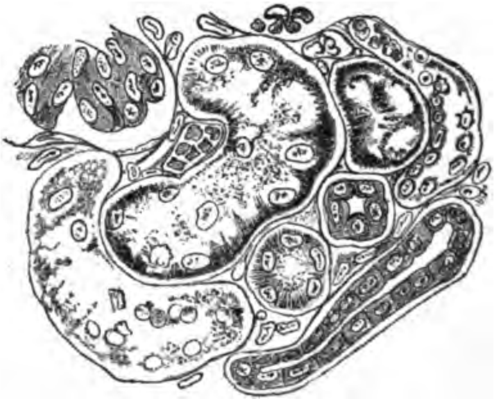

FIG. 77.—Rabbit's kidney after salol-poisoning (Kobert).

Carbolic acid *prevents putrefaction*, or the development of bacteria, in the strength of ½ to 1%.

For the production of surgical antisepsis, too much stress must not be laid upon the fact that it does not kill the organisms in even much greater concentration; for the prevention of their growth is all that is required in the treatment of open wounds.

Phenol, salicylic acid, and other coal-tar antiseptics also have a retarding effect upon *ferment action* — especially carbolic and salicylic acid — somewhat after the manner of quinin. A 5% solution of phenol suffices to materially weaken the action of most ferments.

It is also claimed that these antiseptics (particularly the phenols and anilin dyes) destroy not only bacteria, but also their toxins. This they do in the test-tube; but it may be doubted whether they have this effect in the great dilution in which they exist in the body. On this theory, however, carbolic acid has been recommended in *traumatic tetanus* (10 c.c., increasing to 25 c.c., of 2% solution per day, in divided doses, subcutaneously).

2. Central Actions.—Very small doses of phenol, as of all the coal-tar antiseptics, produce at first an *analgesic and antipyretic action* (see Antipyretic group). This is, however, so fleeting, and passes so readily into the graver effects, that it cannot be used in therapeutics. This preliminary stage is followed by more pronounced symptoms of *excitation,* shown in frogs or mammals by muscular tremors, twitchings, and convulsions.

Carbolic acid causes in the frog a short stupor, followed by incoordinated clonic convulsions. The latter involve the entire central nervous system. Intactness of the sensory paths is necessary for their production, so that they, like those of strychnin, rest upon an increased excitability. The action differs from that of the latter poison in its wider distribution, and in the more incoordinated spasms. Direct application of dilute solutions to the spinal cord of frogs paralyzes the sensory cells (Baglioni, 1900).

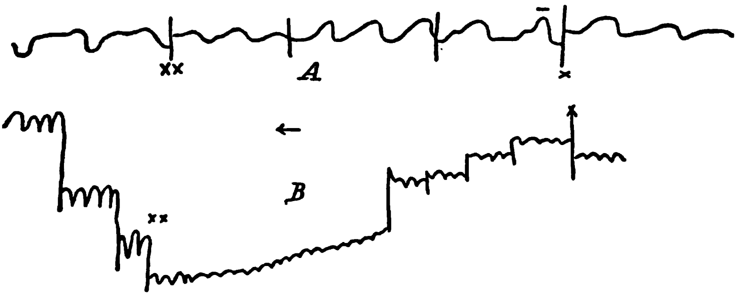

Fig. 78.—Carbolic acid (begins at X) and sodium sulphate (begins at XX). Dog. *A,* respiration (from tracheal cannula); *B,* carotid pressure. The pressure indicates vasomotor paralysis. This and the dyspnea are at once relieved by sodium sulphate.[1]

There are also signs of stimulation of the medullary centers, especially that of *respiration.* The *heart* is quickened and strengthened, probably by a direct action on the cardiac muscle. The *blood pressure* rises in consequence, and also by the convulsions and the direct effect on the vasomotor center. The rise is neither large nor lasting.

In the collapse stage the *heart* is weakened and slowed—presumably by direct action on the muscle. There is *paralysis of the vasomotor center,* and in consequence *fall of blood pressure* (Fig. 78 *B*). The *respiration* becomes slow and shallow, and finally ceases. The *temperature* falls. The phenomena bear a very close resemblance to those of surgical shock. Since the collapse affects all the medullary centers, and the cardiac muscle as well, it cannot, of course, be removed by artificial respiration. This constitutes an important difference to the collapse produced by the drugs of the alcohol series. Another difference consists in the fact that with the antiseptic group the *sensibility to pain* is often *preserved* far into the collapse. In an early stage there is a *mental excitation* with hallucinations, seen especially with salicylic acid. The collapse action is strongest with carbolic acid and creosote, much less with salicylic acid, and very small with benzoic acid.

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[1] Exercise 59.

The local effects of the phenol play no part in the production of the collapse (Sollmann and Brown, 1906). Even small doses, when injected intravenously, cause a prompt and extensive fall of blood pressure, but this recovers again very promptly.

Carbolic acid causes an increase of *secretions*, especially of saliva, sweat, and tears, not yet accounted for. Symptoms of *cinchonism* also sometimes make their appearance after carbolic and especially salicylic acid. Peripherally, *muscle- and nerve-fibers* are killed by the direct application, but do not seem to suffer when the drugs act systemically. Carbolic acid is of value as a *local anesthetic* (5% ointment), especially in itching skin diseases or pruritus.

3. Toxicology.— Suicidal poisoning by carbolic acid is very common, particularly in the United States. Accidental poisoning is also common; it may result even when the phenol is applied to the intact skin; its liberal application to open surfaces has frequently led to toxic symptoms. The *fatal dose,* by mouth, depends greatly on the concentration. 0.8 Gm. has been given therapeutically without bad effects.

Symptoms.— The *local symptoms* consist in burning of the mouth and throat, nausea and vomiting, abdominal pain. The carbolic burns generally heal promptly, with small tendency to scar formation.

The *systemic symptoms* are those of a very speedy *collapse,* starting in a few minutes, even when the drug is taken by mouth. It is manifested by faintness and muscular weakness; sometimes twitching and convulsions; pulse small, weak, and slow; face livid; cold sweat; respiration slow and shallow; unconsciousness; coma; death by stoppage of respiration.

The course of carbolic acid poisoning is *very rapid.* In almost all fatal cases death ensues inside of twenty-four hours.

Chronic Carbol-poisoning.— In the days of the Lister spray, chronic phenol-poisoning was not at all uncommon amongst surgeons. It presented the general symptoms of marasmus. The quantity of the acid entering the system under these circumstances is quite phenomenal: 2 Gm. of phenol were recovered from the urine of a surgeon who had assisted for two and a half hours at an operation under a 2% spray.

Diagnosis.— Besides the course of the symptoms noted, the *odor* of the patient is characteristic. The *urine* is dark and smoky, and gives little or no precipitate with *barium* *chlorid.* The carbolic acid usually exists in the urine combined with sulphuric or glycuronic acid, and is free only in the very gravest cases. To demonstrate its presence by chemic tests, the urine must be *acidulated and distilled,* and the distillate tested.

Treatment.— The *local effects* of phenol are effectively removed by *promptly* washing with alcohol (or whiskey) and applying an oil dressing.[1]

With *internal poisoning,* the greatest success is obtained by extensive *lavage* of the stomach (taking care that the fluid does not enter the trachea). The first washings may be performed with 10% alcohol. *Lime* forms an insoluble compound, and lime water, or better, the syrup of lime, has been used. Potassium *permanganate* also destroys the phenol. Sulphates have been given with the object of forming the non-toxic phenolsulphonates. This combination does not occur in the alimentary canal, and the sulphates are very slowly absorbed, so that the oral administration is useless except in chronic poisoning. The combination is so slow, that it is practically not available in acute poisoning, even if the sulphate is injected intravenously (Brown and Sollmann, 1906). The hypodermic or intravenous injection of the sulphate (½ to 2 liter of a 2.3% solution of the dry salt or of a 4.6% solution of the crystals) is, however, often of great benefit, by its stimulating effect. (Fig. 78, B.) The patients sometimes recover from deep coma during the infusion.

It has been claimed that alcohol is a chemic antidote to phenol, effective even when left in the stomach. Both the clinical and the experimental evidence disprove this view (Clarke and Brown, 1906). Its action is purely mechanical, as described above.

4. **Phenol Compounds.**— The great toxicity of phenol, its very pronounced local irritant action, and its rapid absorption, all lessen very greatly its therapeutic value, and active search has been made for compounds devoid of these undesired properties. The following methods have been tried:

1. By substituting an acid radicle for an H in the C_6H_6 of the phenol relatively non-toxic compounds are produced. Such are the phenolsulphonates, *e. g.,* $C_6H_4{<}\substack{SO_3Na\\OH}$ This combination is, however, useless, since it destroys the antiseptic power as well. *Aseptol* is a mixture of similar sulpho-phenols, obtained by acting on carbolic

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[1] Exercise 18C.

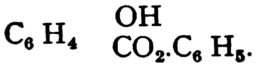
acid with sulphuric acid and adding alcohol. It is indeed antiseptic, but only because it dissociates very readily into its ingredients. It possesses absolutely no advantage over ordinary carbolic acid.

2. By combining the carbolic acid with *proteids:* the resulting compounds do not give up their carbolic acid at all readily, and are therefore of little value.

3. By the substitution of an H of the C_6H_5 by CH_3, producing the cresols (see below).

4. By an ester-like combination with an acid. The resulting compound is inactive, but is decomposed in the alkaline medium of the intestine by the pancreatic enzymes and by the bacteria, liberating its ingredients. The original compound of this class, Salol, is still the most valuable.

Salol is the phenyl salicylate:



$C_6H_4\begin{matrix}OH\\CO_2.C_6H_5\end{matrix}$.

It is but very sparingly soluble in water, and produces by itself no antiseptic qualities. Its use as antiseptic dusting powder is therefore irrational. Used internally, it passes the stomach unaltered, but in the intestines it yields slowly carbolic acid and sodium salicylate. The slowness of this process permits the carbolic acid to exert a full local antiseptic effect throughout the intestine, without danger of flooding the organism with phenol. The salicylate of sodium takes no part in the local action, but is absorbed, and in its passage through the body it exhibits the salicylic acid action.

5. MATERIA MEDICA OF THE PHENOL GROUP.

Phenol (U. S. P.) [**Acidum Carbolicum,** B. P.] (Hydroxybenzene). C_6H_5OH. Colorless crystals, acquiring a reddish tinge, due to unknown and unimportant impurities.

Preparation: The coal-tar separated in the process of purifying illuminating gas is subjected to fractional distillation. The portion distilling between 140° and 220° C. is used for Carbolic Acid; it is treated with 10% NaOH, which dissolves the carbolic acid in the form of a sodium carbolate, whilst the impurities remain insoluble. The carbolic acid is then precipitated from its solution by HCl, and washed. This product still contains other substances (especially cresols), and has a reddish color and a very disagreeable odor. It constitutes the "Crude Carbolic Acid." This furnishes the pure by repeated fractional distillation.

Phenol may also be prepared synthetically from benzol.

Phenol is very faintly acid to litmus, but is not a true acid, either chemically or physiologically.

Pure carbolic acid melts at 42° C. It is soluble at 25° C. in 19.6 parts of water, freely soluble in Glycerin, Alcohol, Ether, oils, etc. Glycerin is the most useful solvent, and aqueous solutions of any strength may be made by adding a sufficient quantity of glycerin.

The crude acid is much less soluble than the pure.

Carbolic acid is but rarely used internally, in *dose* of 0.065 Gm. = 1 gr. (U. S. P.), largely diluted, as antipyretic and intestinal disinfectant. It is not well adapted for either purpose. Its principal use is as disinfectant.

For *disinfecting* instruments or hands, the saturated aqueous solution (containing about 5%) is used; for washing wounds, the 3%; for gargles, lotions, and injections, 1%.

Carbolic acid acts scarcely at all antiseptically when in oily solution. But carbolated oil and ointment are useful local anesthetics, dermal irritants, and promote healing. An ointment made from crude carbolic acid is still more effective.

The inefficiency of the oily solutions is due to their great solvent power for phenol, preventing its transfer to the bacterial protoplasm. Alcohol and glycerin have a similar restraining action. The solubility in petrolatum is very small, so that ointments made with this base should be very actively antiseptic and irritant.

The crude acid is mainly employed as a cheap and efficient disinfectant; the crystallized acid is sometimes employed as a caustic, especially in dental practice.

Preparations:

Phenol Liquefactum (U. S. P.) [*Ac. Carbol. Liqu.,* B. P.].— Made by melting phenol and adding 10% water. (Phenol may be mixed with less than $^1/_{10}$ or with more than 20 parts of water, but not with quantities comprised within these limits.)

Glyceritum Phenolis (U. S. P.) [*Glycerinum Ac. Carbol.,* B. P.].— 20%. Useful for making strong solutions.

Unguentum Phenolis (U. S. P., 3%) [*Ung. Ac. Carbol.,* B. P., 4%]; made with white petrolatum.

Suppositoria Acidi Carbolici (B. P.) (against pruritus).— 1 grain.

* *Oleum Carbolisatum.*— 5%.

Trochisci Acidi Carbolici (B. P.).— Each 1 grain.

The **Phenolsulphonates** (Sulphocarbolates) are neither as toxic nor as irritant as carbolic acid. However, they have also lost much of its antiseptic effect. The sodium salt is sometimes given to control intestinal fermentation, but would seem to be surpassed by other intestinal antiseptics. The zinc salt may replace the zinc sulphate as astringent.

Sodii Phenolsulphonas (U. S. P.) [*Sod. Sulphoarbolas,* B. P.].— $C_6H_4(OH)SO_3Na$ 1 : 4 + $2H_2O$. Sol. in 4.8 water, 130 alc. *Dose:* 0.25 Gm. = 4 gr. (U. S. P.).

Zinci Phenolsulphonas (U. S. P.) [*Zinci Sulphocarbol.,* B. P.].— $(C_6H_4(OH)SO_3)_2Zn + 8H_2O$. Sol. in 1.7 water or alc. *Dose:* 0.125 Gm. = 2 gr. (U. S. P.).

Phenylis Salicylas (U. S. P.) [**Salol,** B. P.].— $C_6H_4(OH)COOC_6H_5$ 1 : 2. Made by heating phenol in the presence of phosphorus pentachlorid. Sol. in 2,333 water, 5 alc. *Dose:* 0.3 to 1 Gm. (5 to 15 grs.) (0.5 Gm. = 7½ grs., U. S. P.) as powders or in capsules.

II. CRESOL GROUP.

The Cresols have the chemical formula $C_6H_4<\begin{smallmatrix}OH\\CH_3\end{smallmatrix}$. The three isomers (ortho, meta, and para-cresol) all occur in the preparations which are usually employed. These are obtained from the residue remaining after the phenol has been separated from the "crude carbolic acid," of which the cresols form the major part. Attention was first directed to their valuable qualities by Fränkel (1889). The introduction of CH_3 into the phenol molecule diminishes its toxicity,

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* Not official.

whilst it increases the antiseptic power. The cresols are about three times as powerful as phenol in disinfecting value, and are said to be only about one-fourth as toxic. Tollens (1905) claims, however, that only meta-cresol is less toxic than phenol; and that the other cresols, and the ordinary mixtures, surpass carbolic acid in toxicity. The paracresol is the most toxic. The local irritant action is very much less: in the concentration in which they are used, they do not blanch or benumb the skin. Their cost is also much less than that of carbolic acid.

The one great disadvantage attaching to them is their very slight solubility in water. This insolubility can, however, be readily overcome. The crude mixture may be emulsified or rendered soluble by soaps or other agents. Or the *pure* cresols may be employed, these being very much more soluble than the crude products.

The cresols are liquids of a peculiar odor, of a color varying in intensity from straw to almost black. The solutions also darken with age, but this does not interfere with their activity. Like phenol, they do not attack metal instruments.

Of the following preparations, only the cresol and the soap-mixtures have attained to any popularity; other solutions are too weak. The soap-mixtures render the hands slippery, and are therefor less valuable than trikresol in operating. They do very nicely for other purposes, and are particularly useful for disinfecting the hands, as they render other soap superfluous (½ to 1% solution, brushing for 2 or 3 minutes). The potash-soaps (Liq. Cresolis Comp.) have an advantage over the resin-soaps in giving clear solutions, instead of turbid mixtures.

Cresol Preparations.— The cresols are used almost exclusively as antiseptics. The *proportions* given below refer to pure cresol. For the mixtures, the proportions should be doubled:

In surgery, ¼ to 1%; gargles or cystitis, ¼%; cuspidors (tubercle bacilli) or stools, 1 to 1½%; for sponging rooms or soaking clothes, ½ to 1%.

To make a 1% solution, add 2 teaspoonsful to a quart of water.

Internal Dose: 0.05 c. c. = 1 ♏. (U. S. P.).

A. Pure Cresols.— *Cresol* (U. S. P.).— $C_6H_4(CH_3)OH$; a mixture of the three isomeric cresols, obtained from coal-tar, freed from phenol, hydrocarbon, and water. Sol. in 60 water, all proportions of alcohol or glycerin. A clear, colorless or straw-colored liquid.

* *Trikresol,* a similar product, contains Orthocresol, 35%; Metacresol, 40%; Paracresol, 25%. Soluble in water to 2.2 — 2.5%.

The isolated cresols are also on the market, but present no advantage over the mixture.

Liquor Cresolis Compositus (U. S. P.).— 50% of cresol, brought into clear solution by a potash-linseed oil soap.

* *Kresamin* (Ethylen diamin — Trikresol; Trikresolamin).— A clear watery solution, containing 25% of ethylendiamin, and 25% of trikresol. Soluble in 1.8 parts of water.

The ethylendiamin increases the penetrating power, and the bactericidal power, so that the latter is about equal to full-strength trikresol. Kresamin has been recommended (as 4 to 20% ointment in lanolin) for eczema and lupus.

B. Preparations of Crude Cresols (Crude Carbolic Acid).— Containing ¼ to ½ of Cresols:

I. Emulsions: turbid, brownish liquids, yielding turbid suspensions with water.

Prepared with:

1. Resin-soap: *Creolin-Pearson; Izal; Cresolin.*

2. Petroleum Oils (the mixture lowering the specific gravity to that of water): *Saprol.*

3. Coal-tar Products (Carbolic Acid, Naphthalin, Pyridin).

II. Solutions: brownish liquids, yielding clear solutions with sufficient water:

Prepared with:

1. Potash Soaps and Alcohol: *Lysol, Lysitol; Lysosolveol; Sapokresol, Phenolin.* (Hard water will precipitate the soap, and cause a turbid solution.)

2. Creosotinate of Sodium: *Solveol, Solutol* (Salicylate of sodium may also be used); Kresooxyacetate of sodium: *Kresin.*

3. Sulfo-acids (Made by heating crude carbolic with equal parts of concentrated H_2SO_4): *Sanatol; Creolin-Artmann* (sulfo-acids of resin and mineral oils may be employed).

III. POLYATOMIC PHENOLS.

It has been stated (p. 357) that the introduction of further [OH] molecules into phenol raises its antiseptic power, but also its toxic and irritant action. *Resorcin* — $C_6H_4(OH)_2$ is useful as a dermal irritant and caustic; *Pyrogallol* is so toxic that it cannot even be endorsed as a parasiticide, for which purpose it has been introduced.

Pyrogallol, however, has a special interest on account of the *methemoglobin formation,* which is produced to some extent by all members of the group, but most intensely by it. Concentrated solutions acting on blood outside of the body produce a peculiar insoluble substance — *hemogallol.* This is never formed in the body; here, and with *dilute solutions* in vitro, the corpuscles become shrunken, crenated, and fragmented, and lose most of their hemoglobin. The latter is partly changed into methemoglobin. The *symptoms* of pyrogallol poisoning are for the most part consequences of this process. It leads to icterus, hemoglobin- and methemoglobin-uria, and a more or less violent nephritis, if the disorder runs a slow course; or cyanosis, dyspnea, and convulsions, if the course is rapid. The *treatment* of poisoning must be symptomatic; large injections of normal salt solution would be indicated.

Resaldol is an insoluble derivative of resorcin and salicylic acid, recommended for the same purposes as resorcin. *Pyrocatechin* and *Hydrochinon,* the isomers of resorcin, are also too toxic to be useful. The latter has, however, important uses when formed within the body:

Uva ursi and *chimaphila* contain a glucosid, arbutin, which is ordinarily excreted unchanged, but is split when it comes into contact with a catarrhal mucous membrane, with the production of hydrochinon, an efficient antiseptic. These plants are therefore valuable urinary disinfectants.

MATERIA MEDICA.

Pyrogallol (U. S. P.) (*Pyrogallic Acid*).— $C_6H_3(OH)_3$ 1 : 2 : 3, obtained chiefly by carefully heating gallic acid. Sol. in 1.6 water, 1 alc. The solutions turn brown, especially in the light. Externally as 1 to 5% ointment (dangerous).

Resorcinol (U. S. P.) (*Resorcin*).— $C_6H_4(OH)_2$ 1 : 3, obtained usually by the reaction of fused NaOH on sodium metabenzenedisulphonate. Sol. in 0.5 water or alcohol. Externally as 10 to 20% solution in glycerin, as cutaneous irritant. Internally, 0.125 to 0.6 Gm. (2 to 10 grs.) (0.125 Gm. = 2 grs., U. S. P.) in fermentative dyspepsia.

Uva Ursi (U. S. P., B. P.).—*Bearberry.*—The leaves of *Arctostaphylos Uva Ursi,* Ericaceæ. Northern Hemisphere. Arbutin and methylarbutin, glucosids, decomposed by water and emulsin with the production of hydroquinon. Inactive glucosid, ericolin, urson, considerable tannic acid. *Dose:* 2 to 4 Gm. (15 to 60 grs.) as infusion (2 Gm. = 30 grs., U. S. P.).

Fluidextractum Uvæ Ursi (U. S. P.).—1/5 alcohol, 1/3 glycerin. *Dose:* 2 c.c. (30 ♏).

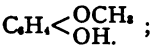
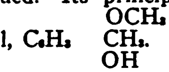
Tinctura Uvæ Ursi (B. P.).—*Dose:* 1/2 to 1 ʒ.

Infusum Uvæ Ursi (B. P.).—5%. *Dose:* 15 to 30 c.c. (1/2 to 1 oz.).

Chimaphila (U. S. P.).—*Pipsissewa; Prince's Pine.*—The leaves of *Chimaphila umbellata,* Ericaceæ. North America. Also contains tannic acid and arbutin. *Dose:* as for uva ursi.

Fluidextractum Chimaphilæ (U. S. P.).—One-half alcohol. *Dose:* 2.0 to 8.0 c.c. (1/2 to 2 drachms) (2 c.c. = 30 ♏., U. S. P.).

IV. Creosote Group.

The empyreumatic products of the distillation of wood—the smoke, and the creosote and tar which may be condensed from it,—possess very considerable antiseptic power. They consist indeed of a mixture of coal-tar derivatives. The most important of these products from a therapeutic standpoint is creosote, the variety which is obtained from beech-wood being particularly valued. Its principal constituents are guaiacol,  $C_6H_4<\begin{matrix}OCH_3\\OH\end{matrix}$; and creosol,  $C_6H_3\begin{matrix}OCH_3\\CH_3\\OH\end{matrix}$. The action of these compounds could be largely deduced from their composition, which is similar to the cresols. They should be more strongly antiseptic and antipyretic, but less irritant and toxic, than is phenol. This is indeed the case. But further than this, clinical experience has assigned to creosote and its constituents certain almost specific actions:

1. In *tuberculosis,* creosote is one of the standard remedies (see Index).

2. In other *pulmonary disease* (bronchitis, pneumonia, etc.) it is similarly useful; but its effect in this case is greatest if it be administered by inhalation, where the local antiseptic and stimulant action can also come into play. Absolutely none is excreted by the lungs (Bufalini, 1904). However, it has been proven that creosote increases the secretion of mucus (also of urine) even when taken by the mouth.

3. It is an efficient *intestinal antiseptic.*

4. In *pleuritic effusions,* it hastens the absorption of the exudate when it is rubbed into the chest.

5. An *antipyretic action* is seen particularly with guaiacol. Ten to fifteen drops of the saturated alcoholic solution, rubbed for ten to fifteen minutes into the clean and dry skin of the abdomen, act as antipyretic. This action is not seen when the drug is taken by mouth, perhaps because it is not absorbed sufficiently.

6. The *local anesthetic* action is also utilized, particularly in dentistry.

Materia Medica of Creosote.—**Creosotum** (U. S. P., B. P.), *Creosote.*—A mixture of phenols, chiefly guaiacol and creosol, obtained during the distillation of wood tar, preferably from the beech (*Fagus sylvatica,* Cupuliferæ; temperate zone). Soluble in 140 water, forming rather turbid solution. Freely in alcohol. *Dose:* 0.03 to 0.12 c.c. (1/2 to 2 minims), preferably in capsules, on full stomach. May be gradually raised to 6 drops if it is well borne (0.2 c.c. = 3 ♏., U. S. P.).

Preparations:

Aqua Creosoti (U. S. P.).—A 1% solution in water. *Dose:* 4 to 15 c. c. (1 to 4 drachms) (8 c. c. = 23, U. S. P.).

Mistura Creosoti (B. P.).—A 0.2% flavored watery solution. *Dose:* as the water.

Unguentum Creosoti (B. P.).—10%.

Guaiacol (U. S. P.).—$C_6H_4(OH)(OCH_3)$ 1 : 2. This constitutes 60 to 90% of creosote and may be prepared from it by fractional distillation or synthetically. A crystalline solid or colorless fluid, of agreeable aromatic odor. Sol. in 53 water, 1 glycerin, all proportions of alcohol. *Dose:* 0.12 to 0.6 c. c. (2 to 10 ♏) (0.5 c. c. = 8 ♏, U. S. P.). It is used *locally* as 50% solution in glycerin for swabbing the throat; or with glycerin and Tr. Iodi for inunction in effusions. Its only advantage over creosote lies in its more constant composition.

* *Creosol* would be more valuable, but its higher cost has precluded its common use.

Creosote Substitutes.—Creosote, and the pure principles possess a number of undesirable properties. They are quite toxic, after the manner of carbolic acid, producing convulsions and collapse in large doses, the convulsions being most pronounced in cold-blooded animals. Guaiacol (but not its carbonate) causes, in very large doses, the appearance of an undetermined, very viscous, substance in the urine, which is supposed to be capable of obstructing the uriniferous tubules. The insolubility and the disagreeble taste of these drugs are also very undesirable.

The irritant properties of creosote and the gastric derangement which it thereby produces are important objections to its use in diseases like phthisis, in which a good digestion is perhaps of equal importance to pulmonary antisepsis. In the endeavor to obviate this, a number of preparations have been introduced.

1. The most useful results have been obtained by producing acid-esters of these compounds, the most important being the *carbonates of guaiacol and of creosote*. As explained under salol (p. 364) such compounds are themselves inactive; they become active only when decomposed into their constituents. In this way the antiseptic is liberated but slowly; its action extends over the entire intestine, but the amount which can be liberated at any time is too small to be either irritant or toxic. The creosote esters are decomposed even more slowly than salol, and indeed only through putrefactive bacteria. They will therefor only become active where their action is required; an excess will pass the intestine unabsorbed. As much as 6 Gm. of Guaiacol carbonate have been given to phthisical patients, as much as 75 Gms. (2½ ounces!) to dogs, without producing toxic symptoms. With these large doses, a great deal of the substance is passed in the feces, without having undergone decomposition. The urine is darkened, but this has no practical significance.

These compounds are very sparingly soluble in water, more readily in alcohol, and in oils (a combination with codliver oil often is useful). They are usually administered either in capsules, or as emulsions (2 or 3 parts of acacia to 1 part of drug). They may also be taken in an egg. In their *administration* the practice is to begin with very small doses (0.2 to 0.4 Gms.—3 to 6 grains or drops)—taken three times a day, ¼ hour after meals. The dose is increased somewhat every second day, until the full therapeutic effect is obtained, and is then kept at this point (usually 25 drops a day). Persistence in the treatment is essential to its success.

Since the liberated creosote or guaiacol are the active portion of these compounds, the acid with which they are combined is absolutely immaterial. The carbonic acid esters are the cheapest and contain the largest percentage of active principles, and therefor deserve the preference which has been universally accorded to them. Similar compounds have been prepared from all other phenols — from thymol, menthol, etc.

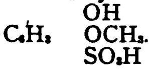
Guaiacoli Carbonas (U. S. P.) (*Duotal*).— $(C_6H_4(OCH_3)O)_2CO$; obtained by the action of carbonyl chlorid on sodium guaiacolate. White, crystalline powder, almost tasteless and odorless; contains 91% of guaiacol. Insol. in water, sol. in 48 alc. *Dose:* 1 Gm. = 15 gr. (U. S. P.) in powders.

* *Creosoti Carbonas* (*Creosotal*), prepared in a similar manner directly from creosote. It is a thick oil, insoluble in water, retaining the odor of creosote. This constitutes an objectionable quality, although this compound is otherwise superior to the duotal. It corresponds to 92% of creosote.

Compounds obtained by the use of other acids are *Phosphatol:* creosote phosphite; *Tanasol:* creosote tannate; *Styracol:* cinnamate; *Benzosol:* benzoate (54%); *Salicylate, Oleate, Geosot:* valerianate; *Guaiasocol* is a diethyl-glycocoll compound.

2. By substituting OC_2H_5 for the OCH_3 of guaiacol, the substance *Guaethol* is obtained. Its action does not differ from that of guaiacol, whilst its preparation is much more expensive.

By substituting another OCH_3 for an H of guaiacol there results the substance *Veratrol*, which is almost inactive, since the [OH], which carries the action of the whole group, cannot be regenerated from this compound. The same is true of the glycerin-ester, *Guiamar*. Replacing an H of the OCH_3 of guaiacol by CO_2H yields *Guaiacetin*, which is also inactive, from the same reason.

3. A compound of a different class is obtained by substituting sulphonic acid for an H of C_6H_4 of guaiacol:  $C_6H_3\begin{matrix}OH\\OCH_3\\SO_3H\end{matrix}$. The potassium salt of this is known as *thiocol*, the calcium salt as *guaiacyl*.

Thiocol differs from the other creosote derivatives in being soluble in both water and alcohol. Even this quality loses in value, for the drug has a markedly bitter taste. But a yet greater objection is, that the action is weak and uncertain. Otherwise it possesses the same properties as guaiacol-carbonate. It is a fine white powder, containing 60% of guaiacol. *Dose:* 1 Gm. a day, raised gradually to 3 Gms.

4. By combination with formaldehyde are obtained *Kreosoform* and *Guaiaform*. The objectionable features of guaiacol are in no way modified in this combination, since the [OH] is not covered. They are quite irrational.

5. Compounds of different composition have been suggested as substitutes for creosote. These lack its most desirable qualities, whilst they are not devoid of its undesired actions.

A cresol solution, *Solveol*, has been used. Whilst it shares some of the actions of creosote, it is in every way inferior.

A number of volatile oils and stereoptens consist of phenols. The most important antiseptic of this type is *thymol*. On account of its "clean" taste, this is a frequent addition to antiseptic mouth washes and gargles. It also finds some uses in the laboratory, since it checks putrefaction without greatly altering ferments or proteids. Its toxicity after absorption is about a fourth of that of phenol, but only a small proportion is absorbed. It has been used against anchylostoma duodenale (2 Gm., repeated in two hours, and followed by Castor Oil).

Thymol (U. S. P., B. P.).— $C_6H_3(CH_3)(OH)(C_3H_7)$ 1 : 3 : 4; a phenol (stereoptene) occurring in the volatile oil of Thymus vulgaris, Carum Ajowan, and some others. Large colorless crystals, of peculiar odor. Liquifies when triturated with camphor, menthol, or chloral. Sol. in 1,100 water, freely in alc. *Dose:* 0.05 to 1.0 Gm. (1 to 15 grs.) (0.125 Gm. = 2 grs., U. S. P.). *Locally* as saturated aqueous solution.

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* Not official.

Liquor Antisepticus (U. S. P.).— A mild antiseptic, containing in 1,000: 20. Boric acid; 1. Benzoic acid; 1. Thymol; 0.25 Eucalyptol; 0.5 Oil Peppermint; 0.25 Oil Gaultheria; 0.1 Oil Thyme; 250 Alcohol. A number of proprietary mixtures, *e. g.*, "listerin," have a similar composition.

Crude Natural Mixtures (Tars).— The following deserve mention:

Pix Liquida (U. S. P., B. P.) [*Pix Carbonis Præparata,* B. P.].— *Pine Tar.*— An aromatic oleoresin obtained by the destructive distillation of pine woods, particularly that of *Pinus palustris,* Coniferæ, United States. *Dose:* 0.5 Gm. = 7½ grs. (U. S. P.). Soluble in alcohol or oils; only partly in water. Tar consists of a mixture of resinous and volatile principles. When it is subjected to redistillation, it can be separated into a fixed portion,— pitch,— consisting mainly of rosin; and a volatile portion which separates into *Oil of Tar* (*Oleum Picis Liquidæ,* U. S. P.) and pyroligneous (crude acetic) acid. The oil of tar consists of various coal-tar derivatives, mainly Cresols, Guaiacol, Phenol, Xylol, Toluol, and Pyrocatechin. It also contains methyl alcohol and acetone. *Dose:* 0.2 c. c. = 3 ♏. (U. S. P.).

Tar is used *externally* as antiseptic, parasiticide, and counterirritant, in the form of:

Unguentum Picis Liquidæ (U. S. P., B. P.).— 50%, in yellow wax and lard.

Internally, it is used in bronchitis, like creosote, and as an expectorant, most usefully as:

Syrupus Picis Liquidæ (U. S. P.).— *Dose:* 4 to 15 c. c. (1 to 4 drachms) (4 c. c. = 13 U. S. P.).

* *Vinum Picis,* N. F.

* *Empyroform* is a formaldehyd-tar compound. It is an insoluble brown powder, which is used as an ointment in the place of tar in the treatment of skin diseases. Its main advantage lies in the absence of odor.

Oleum Cadinum (U. S. P., B. P.) (*Oleum Juniperi Empyreumaticum*).— *Oil of Cade.*— The tar obtained from *Juniperus Oxycedrus,* Coniferæ, Mediterranean. Used *externally* like tar, having a less unpleasant odor.

V. Coal Tar Dyes.

The striking phenomenon of bacteria and tissues "fixing" stains, suggested the somewhat crude idea that this must be connected with a specific toxicity to such bacteria. This is by no means the case. Antiseptic and coloring power are two very distinct properties, which may indeed be coexistent, but which are in no way interdependent. These dyes, belonging to the coal-tar group, share in the general antiseptic action. But the coloring power, which was the original impetus to their employment, interferes with their usefulness. The staining of the urine, the linen and bandages, the hands of the operator, etc., are very undesirable. To this comes the fact that, when prepared as dyes, they are often so impure as to be unfit for medicinal use. Yet confusion of the dye and the medicinal drug is far from uncommon, *e. g.*, with Methylen Blue.

Methylthioninæ Hydrochloridum (U. S. P.).—**Methylene Blue** (medicinal) (*not to be confused with methyl blue!*).— $C_{16}H_{18}N_3SCl$; readily sol. in water or alc. *Dose:* 0.02 to 0.25 Gm. (⅓ to 4 grs.) (0.25

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Gm. = 4 grs., U. S. P.). *Externally,* in 0.5% solution for mucous membranes; in 2% for skin.

The drug has been used considerably as an analgetic and antipyretic in neuralgia, neurites, and sciatica; as an antipyretic; in cystitis, urethritis, conjunctivitis, and in skin diseases; as an antizymotic in malaria. It paralyzes the malarial plasmodia even more powerfully than does quinin, but in practice it has not proven a very useful substitute for the alkaloid. It sometimes produces gastro-intestinal irritation, vesical spasm, and excessive diuresis. It is sometimes used as a diuretic.

* *Fuchsin* is quite strongly antiseptic, and very little toxic, but has not been greatly used.

* *Pyoktaninum Cæruleum* (Methyl Violet)
* *Pyoktaninum Aureum* (Auramin)
} Externally, as disinfectant, 1 to 4: 10,000, or 2% ointment.

The methyl-violet is the stronger antiseptic and the less toxic (Stilling, 1890). It has also been used in inoperable malignant tumor, it being claimed that it causes the neoplasm to disappear.

* *Acidum Picricum.— Picric Acid.— Trinitrophenol,* $C_6H_2.(NO_2)_3.OH$. *Preparation:* Nitration of Phenyl-sulphuric Acid by Nitric Acid. Yellow crystalline powder of very bitter taste, soluble in 90 parts water, more readily in alcohol. The watery solution stains organic substances an intense yellow. Now obsolete in medicine. Whilst it is quite strongly antiseptic and anesthetic, it is very toxic. If absorbed, it destroys the red corpuscles, and produces nephritis, convulsions, and death through paralysis of respiration.

Benzosulphonidum (*Saccharin*): This substance (see Index) acts as a protoplasmic poison and restrains all ferments, especially the salivary and pancreatic, and probably the oxidations within the body. Large doses cause headache, depression, stupor, convulsions, and nephritis. It is promptly and completely excreted unchanged (Mathews and McGuigan, 1905).

VI. Salicylic Acid Group.

The salts and esters of salicylic acid are practically inactive outside of the body; at least, their antiseptic action is insignificant. Systemically, however, they produce equal effects, the salicylic acid being liberated by the carbonic acid of the blood. The free acid is markedly antiseptic.

Actions.— The effects of salicylic acid differ from those of phenol by a *lesser action on the central nervous system.* The *convulsive action* is almost absent, and the collapse action much weaker than with carbolic acid. The *antipyretic* and analgesic effects are more conspicuous. The antiseptic effects differ from those of phenol by the *lesser penetration* on account of the non-volatile nature of the substance. The *irritant effects* are weaker, except in the case of the free acid. However, all salicylates have a *nauseant taste* and produce considerable gastric irritation.

Large doses sometimes cause *abortion.* They are therefore contra-indicated in pregnancy.

Injected intravenously into animals, methyl and ethyl salicylates cause pulmonary edema through injury to the capillary walls.

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* Not official.

Salicylates increase the flow and secretion of *bile.* They are slightly *diuretic,* perhaps through renal irritation. The *excretion* of sulphates, of *nitrogen,* and especially of *uric acid* is increased, to such a degree that it must be attributed to an increased destruction of proteids, and not simply to the diuresis. According to Hall (1904) the excretion of *endogenous purins* is increased, not by increased production, but by lessened destruction. (The increase of uric acid excretion, which was claimed for benzoic, salicylic and quinic acids (Weiss, 1898), has not been confirmed by some recent observers (Hupfer, 1903; Taltavall and Gies, 1903).) Salicylic acid does not affect the *absorption of fat or proteids.* The *leucocytes* of the blood are doubled an hour after taking salicylates, but return to normal within two hours. The *excretion of salicylic acid* is usually completed in 25 hours. Large doses color the urine green. For the *fate* of the acid, see below.

The distribution of salicylic acid in the body is extensive. Traces are present in all organs, but the greatest quantity is found in the blood and joints, especially in infected animals (Bondi and Jacoby, 1905).

Poisoning by salicylates is rare; the cinchonism indicates sufficiently when the administration has been carried far enough. The treatment is entirely symptomatic. No bad effects have ever been referable, with certainty, to the use of salicylic acid as a *food preservative;* but it is not improbable that such exist.

Therapeutic Uses.— The salicylates are used principally in *acute articular rheumatism,* where their effect is so specific that they have a diagnostic, as well as a therapeutic value. They allay the pain, fever and swelling almost immediately, when they are administered in sufficient quantity. They have no effect on the course of the endocarditis if this has started before the salicylates are begun. They are nearly as effective in acute muscular rheumatism. In chronic rheumatism they are practically useless. Salicylates are also used against headache and as antipyretic. Free salicylic acid is an efficient preservative. Its softening action on the epidermis is utilized in skin diseases (ointments) and in "corns" (dissolved in collodion).

Administration.— For *internal use,* the free salicylic acid is too irritant. The sodium salicylate is the most commonly used, notwithstanding its mawkish, nauseant taste. This may be partly disguised by giving the salt in carbonated water, or by the addition of glycerin (4 parts of this to each of the salicylate), flavoring with peppermint or wintergreen water.

To be effective in acute rheumatism, large doses must be administered: 1 to 1.3 Gm. (15 to 20 grains) should be given every hour, until the ears ring (requiring a total of 15 to 20 Gms., 200 to 300 grains; this often causes some delirium). The administration should then be stopped for twelve hours. After this, 1 Gm. (15 grains) should be given every four hours for several weeks, keeping the patient in bed as long as possible. As a prophylactic treatment, 1 Gm. (15 grains) may be given three times a day for a week in every month.

If the sodium salicylate is not tolerated, oil of gaultheria or aspirin may be substituted. Somewhat larger doses will be required. Oil of gaultheria also gives some relief when applied externally to the affected joints. (If these esters are also objectionable, recourse must be had to the much less efficient antipyrin, 1 to 2 Gm., three times per day.)

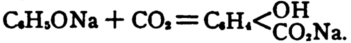
In very severe cases, the *intravenous injection* of sodium salicylate may be justified. Mendel (1905) uses 2 c.c. of a solution containing 16% of the salicylate and 4% of caffein, every twelve hours for three days.

Salicylic Acid Derivatives.— The *disagreeable qualities* of the salicylates depend mainly upon their local irritant action, and consist in a nauseant taste and in gastric irritation. Vomiting may ensue, and render their use impossible. Cinchonism may also set in. These features may be removed by the use of insoluble compounds which are inactive as such, but from which salicylates are slowly split off in the intestine. The first synthetic compound of this kind to be used, was *Salol.* This is not, however, ideal, for the liberated phenol exerts its own action, which is too powerful, when only the salicylic acid action is wanted. The combination with inactive radicles is then much more useful. A compound of this kind is *methyl-salicylate,* $C_6H_4<\genfrac{}{}{0pt}{}{OH}{CO_2.CH_3}$ which exists naturally as oil of wintergreen and as oil of sweet-birch, but which is also prepared synthetically, the last being the least irritant. Methyloxymethylsalicylate (*mesotan*) is a similar product. Another natural compound of this order is *Salicin,* a glucosid, which on decomposition in the intestine yields *Saligenin,* $C_6H_4<\genfrac{}{}{0pt}{}{OH}{CH_2OH}$ (salicylic alcohol), and this is readily oxidized to salicylic acid. *Salophen,* $C_6H_4<\genfrac{}{}{0pt}{}{OH}{CO_2.C_6H_4.N.H.COCH_3}$ belongs to the same general type, being formed by the combination of salicylic acid and acetanilid.

In all these compounds, the substitution occurs in the CO_2H group. The OH may also be replaced; but most of the products of the latter class regenerate salicylic acid so slowly as to be useless. Acetyl Salicylic Acid (*Aspirin*) $C_6H_4<\genfrac{}{}{0pt}{}{C_2H_3O_2}{CO_2H}$ is a notable exception; it produces a fair systemic action with a minimum of local irritation.

Materia Medica of Salicylic Acid.—Acidum Salicylicum (U. S. P., B. P.).—*Salicylic Acid.* $C_6H_4(OH)COOH$ 1 : 2.

Preparation: (*a*) Synthetically, by the action of CO_2 on sodium carbolate, according to the end-reaction:



$$C_6H_5ONa + CO_2 = C_6H_4<\genfrac{}{}{0pt}{}{OH}{CO_2Na}.$$

This sodium salicylate is decomposed by HCl.

(*b*) From oil of wintergreen (methyl salicylate) by saponification with an alkali.

It is sometimes claimed that the salicylates prepared from wintergreen are much superior to the synthetic; but there does not appear to be any strong proof of this assertion.

Characters: A white, light, crystalline powder or needles of a sweetish taste, producing sneezing when inhaled. Soluble in 308 parts water or 2 parts of alcohol.

Uses: Externally as disinfectant in mouth-washes, etc.; for destroying epidermis, etc. (corns); for preserving food substances, ½ to 6 per 1,000.[1] Internally it has been replaced by the salicylates. *Dose:* 0.5 Gm. =7½ grs. (U. S. P.).

Unguentum Acidi Salicylici (B. P.).— 2%.

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[1] Salicylic compounds occur naturally in a number of fruits, so that their presence in jams, etc., does not necessarily prove that they have been added as preservatives.

**Collodium Salicylatum Compositum* (N. F.), a corn preparation. It contains 11% of the acid, Extract of Cannabis ind., and flexible collodion. It is applied at night and the corn is scraped in the morning.

Salicylates.— White powders or crystals, turning pink on exposure; disagreeable sweetish taste. The solutions soon acquire a brown color. Freely soluble in water, alcohol, and glycerin; Strontium salicylate less so. *Dose:* 0.3 to 2.0 Gm. (5 to 30 grs.) (1 Gm. = 15 grs., U. S. P.), in solution.

1 part of salt is soluble in	water	alcohol
Sodii Salicylas (U. S. P., B. P.).— $NaC_7H_5O_3$........	0.8	5.5
Ammonii Salicylas (U. S. P.).— $NH_4C_7H_5O_3$.........	0.9	2.3
Lithii Salicylas (U. S. P.).— $Li.C_7H_5O_3$..............	Very soluble	
Strontii Salicylas (U. S. P.).— $Sr(C_7H_5O_3)_2$.........	18.	66.

Salicylates are *incompatible* with acids.

Salicylic Esters.— *Methyl Salicylate* ($CH_3.C_7H_5O_3$) exists in three forms:

As a synthetic product: *Methyl Salicylas* (U. S. P.).

As the volatile oil of *Betula lenta: Oleum Betulæ Volatile* (U. S. P.). — *Oil of Sweet Birch.*

As the volatile oil of *Gaultheria procumbens: Oleum Gaultheriæ* (U. S. P.).— *Oil of Wintergreen.*

The *dose* of these is 0.06 to 1 c. c. (1 to 15 minims) (1 c. c. = 15 ♏, U. S. P.). Sol. in all proportions of alcohol; very sparingly in water. They are less irritant and disagreeable, but also much less active, than the sodium salicylate.

**Aspirin* (Acetyl-salicylic acid).— White needles, acidulous taste. Sol. in 100 water. Incompat. with alkalies. *Dose:* 1 Gm. (15 grs.), in powders.

**Mesotan* (Methyloxymethyl-salicylic acid).— Clear, yellow, faintly aromatic fluid, almost insoluble in water; sol. in alc. and in oils. Readily absorbed by the skin from its oily solution. It is used by rubbing a teaspoonful of a mixture of equal parts of mesotan and olive oil into the skin at the site of the rheumatic pain (Dreser, 1903).

Phenylis Salicylas (Salol).— See Index.

**Salophen* (Aceto-para-amido-salol).— Colorless crystals, insoluble in water, soluble in alcohol. *Dose:* 1 to 2 Gm. (15 to 30 grs.).

Salicinum (U. S. P., B. P.).— $C_{13}H_{18}O_7$; a glucosid derived from several species of willow and poplar. *Soluble* in 21 parts of water or 71 of alcohol. *Dose:* 0.3 to 2.0 Gm. (5 to 30 grs.) (1 Gm. = 15 grs., U. S. P.).

VII. OTHER AROMATIC ACIDS.

We have just seen how the simultaneous presence of OH and CO_2H gives very valuable antiseptic qualities to the benzol ring. For this purpose the two groups must be in ortho-position; the para and meta-isomers being inactive.

In *Benzoic acid,* there is substitution of CO_2H alone. This compound (and its salts) are almost devoid of antiseptic or toxic qualities.

Acidum Benzoicum (U. S. P., B. P.).— *Benzoic Acid.*— $C_6H_5CO_2H$. Prepared by treatment of Toluol ($C_6H_5CH_3$) with Chlorin and heating with water to 150° C., or by sublimation of Gum Benzoin. Soluble in 28 parts of water and 1.8 parts of alcohol. *Dose:* 0.5 Gm. = 7½ grs. (U. S. P.). Externally, as ointments, 5 to 10%; as wash, 1% (with addition of alcohol).

Trochiscus Acidi Benzoici (B. P.).— Each ½ grain.

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* **Not official.**

Benzoates.— White powders or crystals, odorless, sweetish taste. Freely soluble. *Dose:* 1 Gm. = 15 grs. (U. S. P.):

	1 part soluble in water	alcohol
Sodii Benzoas (U. S. P., B. P.).— $NaC_7H_5O_2$	1.6	43.
Ammonii Benzoas (U. S. P., B. P.).— $NH_4C_7H_5O_2$	10.5	25.
Lithii Benzoas (U. S. P.).— $LiC_7H_5O_2$	3.	13.

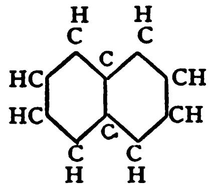
Cinnamic Acid, $C_6H_5.CH = CH.CO_2H$, has also very little antiseptic action or toxicity, but specific qualities are claimed for it in tuberculosis (see Index).

**Sodii Cinnamas* (Hetol).— Used in tuberculosis. Formerly given intravenously, now often hypodermically, 3 to 20 c. c. per day of a 4% solution, continued for 3 to 6 months.

The aromatic balsams — Balsam of Peru and Copaiba, Styrax, Tolu, Benzoin, etc.— also owe their activity largely to members of this series; benzoic and cinnamic acid, etc. They are discussed in Chapter XXIX.

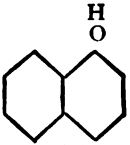
VIII. NAPHTHALIN DERIVATIVES.

Naphthalin:

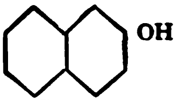


= *Naphthalin* $C_{10}H_8$

This compound is but slightly antiseptic, although it produces toxic effects. The introduction of OH, forming *Naphthol,* gives it an antiseptic action. Two isomers exist:

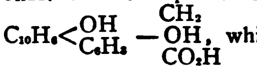


Alpha.



Beta.

The *alpha* is far more toxic and is not employed in practice. The *beta* is very little soluble in water, and its use is restricted to intestinal antisepsis and to dermatology. Its sodium compound $C_{10}H_7ONa$ is soluble, and is known as *Mikrocidin.* The beta naphthol possesses, like all phenols, some irritant properties, which can be removed by replacing the OH by acids, producing salol-like esters. The naphthol is slowly liberated from these in the intestine. The most useful compound of this class is the naphthol benzoate, $C_6H_5CO_2.C_{10}H_7$, known as *benzonaphthol.* This also causes diuresis. By replacing an H of the $C_{10}H_7$ of the naphthol by the oxytoluic radicle, an acid is obtained,



$C_{10}H_6{<}{\begin{matrix}OH\\C_6H_3\end{matrix}} - \begin{matrix}CH_3\\OH\\CO_2H\end{matrix}$, which is known as *epicarin.* It is strongly antiseptic, but little irritant, and is used externally against parasitic skin diseases.

Quinolin is strongly antiseptic to bacteria (although it has no action on yeast), but is too toxic to be useful. The introduction of a methyl or other alkyl radicle increases the antiseptic power. A derivative has been introduced under the name of *Oxychinaseptol* or *Diaphterin,* but it has not become popular. It blackens metallic instruments.

Materia Medica.— Naphthalenum (U. S. P.).— $C_{10}H_8$; colorless crystalline powder, insoluble in water, sol. in 13 alc.; coal-tar odor and hot taste. *Dose:* 0.1 to 0.5 Gm. (2 to 7 grs.) (0.125 Gm. = 2 grs., U. S. P.).

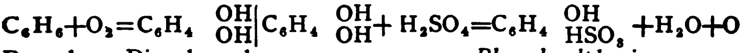
Beta Naphthol (U. S. P.) [*Naphthol,* B. P.].— $C_{10}H_7OH$; resembles naphthalin in physical characters. Sol. 950 water, 0.61 alc. *Dose:* 0.2 to 1.0 Gm. (3 to 15 grs.) (0.250 Gm.=4 grs., U. S. P.). (The administration of this substance has been observed to produce changes in the retina and opacity of the lens.)

* *Benzonaphthol.*—A white crystalline powder, free from odor or taste; insoluble in water, sparingly in alcohol. *Dose:* 5 Gms. (75 grs.) per *day*, in divided doses of 0.5 Gm. (8 grains) every two hours, as powders.

* *Epicarin.*—Colorless or yellowish needles, very little soluble in water, easily in alcohol or oils. Used in 10 to 20% ointment; or in 10 to 50% alcoholic solution.

IV. FATE OF THE COAL-TAR DERIVATIVES IN THE BODY.

The aromatic compounds tend to undergo oxidation in the body; but this affects in almost all cases the hydrogen atoms or side-chains only, leaving the carbon atoms of the ring intact, and preserving the form of the latter. This results in hydroxyls or acid groups. These new compounds again enter into combinations,—those containing hydroxyl groups with sulphuric and glycuronic acids; those containing acid radicles with glycocoll. A few formulas will illustrate this:



$$C_6H_6+O_2=C_6H_4\begin{matrix}OH\\OH\end{matrix}\Big|\,C_6H_4\begin{matrix}OH\\OH\end{matrix}+H_2SO_4=C_6H_4\begin{matrix}OH\\HSO_3\end{matrix}+H_2O+O$$

Benzol Dioxybenzol *Phenol-sulphuric Acid.*

$$C_6H_5.OH + HCO_2.(CH.OH)_4.COH = C_6H_5.CO_2.(CH.OH)_4.COH + H_2O$$

Phenol. Glycuronic Acid. Phenol-glycuronic Acid.

$$HC_7H_5O_3 + C_2H_5NO_2 = HC_9H_8NO_4 + H_2O$$

Salicylic Acid. Glycocoll. Salicyluric Acid.

$$HC_7H_5O_2 + C_2H_5NO_2 = HC_9H_8NO_3 + H_2O$$

Benzoic Acid. Hippuric Acid.

There are considerable differences in detail; other products are formed along with those given, such as hydrochinon, pyrocatechin, etc., whose oxidation products give rise to the characteristic dark color of the urine. These products have not been thoroughly studied, but some are closely related to humin. (Picric acid gives the urine a peculiar red color; Walko, 1901.)

The formation of these combined acids is of considerable practical importance. They are much less poisonous, and their production is in that measure a protective mechanism, whose efficiency can be increased by the administration of soluble sulphates. They also form an index to the gravity of the poisoning. The phenol sulphates do not precipitate with barium, and hence so long as the urine gives a precipitate with the latter, it is a certain indication that the organism is able to cope with the poison. But when the precipitate becomes very small or disappears, the sodium sulphate should be pushed rapidly. These compounds also reduce copper, and may therefore be mistaken for sugar. The reduction usually occurs only after standing some time, if it is due to these compounds.

The principal ***drugs which cause the appearance of reducing substances,*** not sugar, ***in the urine*** are: Turpentine, chloroform, chloral, phenacetin, saccharin, salicylic acid, balsams.

V. METHEMOGLOBIN FORMATION.[1]

In describing the coal-tar products, we have frequently had occasion to mention the formation of methemoglobin by them.

Methemoglobin has the same elementary composition as oxyhemoglobin, but the two differ very essentially in certain of their properties:

1. The spectrum (see Fig. 79). The color of methemoglobin has more of a brownish tinge.

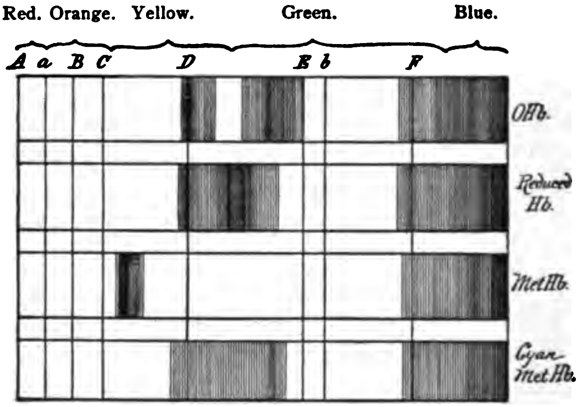


FIG. 79.— Spectroscopic band of blood pigments.

2. In the readiness with which they give up oxygen. Whilst the oxyhemoglobin is a very unstable compound, giving up its oxygen and taking it again, with great readiness, methemoglobin is a comparatively stable and unchangeable compound.

3. In their behavior to certain reagents. For instance, HCN does not form any characteristic compound with oxyhemoglobin, but with the methemoglobin it gives cyanmethemoglobin. Similar compounds are formed with H_2O_2, sulphocyanids, and many other salts, and also with alkalies.

Methemoglobin may be formed from oxyhemoglobin in quite a number of different ways:

1. By oxidizing agents: $KClO_3$; Pot. ferricyanid; Pot. permanganate, H_2O_2, etc.

2. By reducing agents: The nitrites, hydroxylamin, formalin, iodin, chrysarobin, etc.; coal-tar products. (Phenylhydrazin also gives reduced hemoglobin, and destroys some of the hemoglobin absolutely, producing a new compound which, under certain conditions, yields a

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[1] Exercise 21. For Bibliography, see Benedicenti, Archiv für Physiologie, 1897, p. 210.

green pigment, hemoverdin. The precipitation of hemoglobin by pyrogallol in shed blood, has been mentioned previously.)

3. In the early stages of putrefaction, and by the action of light.
4. By salts and glycerin.
5. By acids (this has recently been denied).

The methemoglobins formed by these different methods were formerly considered identical. Lately it has however been demonstrated that their spectra show certain differences.

The physiologic significance of this methemoglobin formation rests on the stability of the compound and its consequent inability to carry out the functions of oxyhemoglobin. This produces asphyxia of the tissues. Pure methemoglobin solutions may be injected into the blood, without causing any symptoms. Even the urine remains free from albumin or methemoglobin. The compound is in part secreted by the bile, in part deposited in the hematopoietic organs.

Nor is the *temporary* conversion of a considerable proportion of the oxyhemoglobin into its isomer of great significance; for methemoglobin is not absolutely stable, and as soon as the oxygen-starvation of the tissues is carried to a certain degree, they seize upon the methemoglobin and decompose it. The conversion of a third of the hemoglobin into methemoglobin causes only very slight symptoms; and life is still possible when three-fifths of the hemoglobin has been replaced. Life becomes extinct when the hemoglobin has sunk to one-third. The condition can therefore become dangerous only if the methemoglobin-former continues its action. This does not occur in therapeutic doses of any of these drugs, but may contribute to the fatal ending in cases of poisoning. The symptoms are those of asphyxia. There is a peculiar blue about lips and finger-nails, etc. The methemoglobin gradually returns to oxy- or reduced hemoglobin after death, so that an examination after several days may fail to reveal its presence.

Most of these drugs transform the hemoglobin inside of the corpuscles, without injuring the vitality of the latter; but some cause, in addition, a breaking up of the corpuscles, and this greatly increases the danger. Aside from the asphyxia which must be proportioned to it, the proteid and other substances liberated cause injury to the kidney — albuminuria, glycosuria, methemoglobinuria, etc. It is also claimed that it causes the sudden formation of fibrin ferment, which may then cause extensive intravascular clotting. The debris is also credited with causing emboli. But these facts are not admitted by all authorities. A small destruction, such as may be caused by the subcutaneous injection of glycerin, certainly has no permanent injurious effect.

The specific action of the drug is, of course, joined to these methemoglobin effects, and may entirely overshadow them. Thus, rabbits die of $KClO_3$ before it comes to any methemoglobin formation. Herbivorous animals are, as a rule, much less subject to the formation of methemoglobin during life, although their shed blood does not differ in this respect from that of carnivorous animals. The cause lies perhaps in the greater alkalinity of their blood, for it has been found that alkali-methemoglobin is much more easily converted back into oxyhemoglobin. The injection of alkalies has therefore been suggested in the treatment of methemoglobinæmia. Other treatment consists in the administration of oxygen, artificial respiration, and shock-treatment.

The drugs which are important as methemoglobin-formers are for the most part discussed in other connections. *Nitrobenzol* may be mentioned here. It has some toxicologic importance since it is used in perfumery and in the arts. It produces the asphyxial effects characteristic of methemoglobinæmia.

(C) DISINFECTION.

I. GENERAL CONSIDERATIONS.

The subject of disinfection has risen to such importance, that it may be well to summarize its principles from a pharmacologic standpoint. This summary cannot take account of all the practical details, for which the student is referred to text-books of bacteriology, surgical technic, and hygiene.

Toxicity and Resistance.— The protoplasm of bacteria is fairly readily injured by many substances and by physical changes. The conditions under which it exists are, however, somewhat peculiar: By virtue of a highly impenetrable cell wall, and by the formation of very resistant spores, bacteria are able to survive conditions which would kill other cells. Under these adverse conditions the microorganisms are indeed unable to grow and multiply; but by passing into a dormant state, particularly by spore formation, they are able to preserve their vitality for a considerable time, and to recover their power of growth as soon as the conditions become more favorable. Substances which merely suspend the vitality of bacteria are called *antiseptics;* whilst those which kill them outright are *germicides.* A third class of disinfectants is formed by the *deodorants,* which obscure or destroy the odorous bacterial products, but which have little action on the bacteria themselves.

Factors Determining Usefulness.— The nature of the antiseptic substance, or the strength in which it is used, are by no means the only factors determining its efficiency and usefulness. Amongst the other more important factors may be mentioned:

1. The *nature of the micro-organism.*

Saprophytes are more resistant than pathogenic bacilli; micrococci than either, and spores most of all.

There also is some *selective action,* some substances being comparatively much more toxic to one species than to another. (Thus, gold chlorid is more toxic to anthrax than to cholera; carbolic acid, the reverse.)

2. The *number of bacteria to be destroyed.*

3. The *nature and quantity of the associated material.* Many substances which are strongly germicidal when acting on the bacteria alone are much weakened by entering into chemic reactions with the medium.

Thus, potassium permanganate is *destroyed* by all organic matter; mercuric chlorid is *precipitated* by proteids; silver nitrate by chlorids, etc. These insoluble combinations are no longer germicidal. Further, they *hinder the penetration* of the antiseptic, a condition of considerable surgical importance. Of all the antiseptics, those of the aromatic series are least acted upon. As we have seen, they do not enter into chemic combination with the media, and have therefore a superior penetrating power.

4. The *time of exposure.* The different antiseptics show great variations ~~in this~~.

5. The *degree of dilution* of the disinfecting agent is in most cases of the greatest importance. A decigram of sublimate in 100 c.c. of water will be much more efficient than a gram in ten liters.

6. The *toxic and corrosive action* of the agent, and the ease with which it is absorbed, are also often of importance in deciding its practical usefulness.

7. The *cost* often enters into consideration.

II. ANTISEPTICS IN COMMON USE.

The more commonly used antiseptics are the following:

Physical Agents: Heat.

Inorganic Salts: $HgCl_2$, $AgNO_3$, $FeSO_4$, $CuSO_4$, $ZnSO_4$, $ZnCl_2$, Al_2Cl_6, $KAl(SO_4)_2$, $NaCl$, KI, NaF.

Acids: H_2SO_4, HNO_3, $HC_2H_3O_2$, H_3BO_3, As_2O_3.[1]

Alkali: CaO.

Oxidizing and Reducing Bodies: SO_2, $KMnO_4$, H_2O_2, O_3, I, Br, Cl, Calx Chlorata.

Fatty Series: $CHCl_3$, CHI_3, CH_2O, C_2H_5OH, $C_3H_5(OH)_3$, sugar.

Aromatic Series: See preceding section. To this may be appended camphor and the essential oils.

Alkaloid: Quinin.

Manner of Action.—Of the inorganic salts, those of the *heavy metals* and of *aluminum* are antiseptic by forming insoluble proteid compounds with the protoplasm of the bacteria. However, they do not probably penetrate the cell-wall very readily. In all cases their action is very greatly weakened if other proteids are present, as they are bound and rendered inactive. The greater number are deodorant, rather than antiseptic, by combining with the H_2S and NH_3 and similar odorous substances.

Of the *neutral salts of alkalies,* the *fluorids,* and to a less extent the *borates,* possess specific toxicity. The effects of NaCl and KNO_3, as also sugar, are due purely to osmotic action. They render the medium unfit for the bacteria and thereby lower their vitality. The *iodids* have no special action, except when iodin is liberated from them.

Bacteria, like all living organisms, require a certain *reaction* of medium for their development; and a considerable modification of this, by either acids or alkalies, is inimical to them. Most forms are more sensitive to acids.

Strong *oxidizers and reducers* tend to produce chemic changes in all organic matter, and bacteria are no exception. However, for this very reason these substances are quickly rendered inactive by any foreign matter which is usually found with these organisms. It can never be hoped to have any action from them after their absorption; and locally only if the amount of organic matter present is small; or apart from the body, if they can be used in sufficient concentration without also destroying the infected article.

The drugs of the *fatty series* are rather weakly antiseptic; their action lies in the precipitation of protoplasm produced by them. Since these precipitates remain for a considerable length of time, capable of being dissolved, they are scarcely at all germicidal. Formaldehyd forms a notable exception to this.

The Disinfecting Power of the Commonly Used Antiseptics.—On account of the different resisting power of different bacteria, and the ease with which the antiseptic action is modified by circumstances, the results of experiments directed to comparing the different antiseptics cannot be generalized. Tables of antiseptic values are therefore unsatisfactory. In a general way, it may be said that mercuric chlorid and silver nitrate are the most powerful. Then come copper and zinc salts; then formaldehyd, chlorin, and hydrogen peroxid; then the cresols, then carbolic acid. Salicylic acid, boric acid, sulphurous acid, and the essential oils are antiseptics rather than germicides. Iodoform manifests its action only under special conditions. Ferrous sulphate is merely deodorant.

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[1] Arsenic is an insecticide rather than a germicide.

Heat, where it can be properly applied, is amongst the most certain of antiseptics. Combustion furnishes the surest method of absolutely destroying bacteria. Boiling, if sufficiently prolonged, or exposure to life steam, especially under pressure, are equally efficient. Exposure to dry heat is less effective.

III. THE PRACTICAL APPLICATION OF ANTISEPTICS.

The Preservation of Food.— The liability of organic food-stuffs, especially meat and milk, to bacterial decomposition, often renders their chemical preservation a matter of economic necessity. Asepsis, refrigeration, or sterilization by heat, are not always applicable. That the use of chemic preservatives is theoretically undesirable, on account of their possible deleterious action, is universally granted; in practice, however, this evil may be less than those resulting from the consumption of partly decomposed foods. The time-honored use of sugar or salt-cured, corned, and smoked meats is a sufficient proof of the comparative innocuousness of some of the preservative measures. More recently there have been introduced a number of preservatives which are more powerful, and which cannot be detected by the taste. These offer a special interest, and they have accordingly given rise to much discussion. It is evident that drugs with markedly toxic and irritant action should be entirely excluded. On this account, the use of formaldehyd has been generally condemned (although the direct proof of its harmfulness is not complete). It has been used, especially in milk, in the proportion of 1 : 25,000. Sulphurous acid, or sulphite of lime, are also considered harmful; but it is claimed by some that they are largely converted into the inactive sulphates; and that the amount escaping decomposition is too small to be serious.

The least harmful of the chemic preservatives are salicylic acid, boric acid, and borax. The acids are used in fluids in the proportion of 0.2 Gm. per liter; in meats 2 or 3 times this proportion is taken. Of borax about four times the above quantities is required. These amounts are too small to kill the bacteria, but suffice to check their development for a limited time. As regards their effects on man, it is universally conceded that these quantities produce no immediate effects in normal individuals. Their opponents rest their objections mainly on their action on weak or diseased individuals, on infants, nephritics, and dyspeptics; and to the cumulative effects of their continued administration. The experimental evidence indicates that these fears are not groundless (see Index, boric acid). There is, however, no evidence as to the degree of danger from their intermittent use, under the actual conditions. At all events, the consumer should be made aware of the addition of the preservative, and of its possible dangers.

The Sterilization of Water.— Drinking water is the ordinary source of infection of a number of diseases, notably typhoid fever. The careful regulation of the water supply, and efficiently supervised filtration are sufficient to remove the danger of infection; but these methods are unfortunately not practicable in all cases. Distillation, or boiling the water for ten minutes, also destroys the typhoid bacilli, but injures the taste of the water. There is therefore some scope for a chemic disinfection of water. The recent experiments of G. W. Moore (1904) indicate that copper may be used for this purpose. This metal combines a high toxicity for lower organisms with a very low toxicity for mammals. It was originally proposed for the removal of algæ from the water supply. A proportion of 1 part in 50 millions suffices for this purpose. Typhoid and cholera bacilli require a much higher proportion (1 : 100,000 for 3 to 4 hours); and it is proposed at present to use the metal for this purpose only as a temporary expedient. The amounts which would be actually taken in the drinking water would be extremely small, as a considerable part of the copper is precipitated in insoluble form. Immensely larger quantities have been taken for several days without any symptoms. The temporary use of the treated water would therefore be certainly harmless. Even the continuous use may be without any effect, although there is as yet no direct evidence on this subject. Kraemer (1904) has recommended the suspension of strips of bright copper, 3½ inches square, for each quart of water, for 6 to 8 hours, as effective for killing the typhoid bacilli, and as being probably harmless to the consumer.

Excreta and Sputa.—A distinction must be made between the sterilization of excreta coming from patients afflicted with contagious disease, and the disinfection of ordinary privy vaults. In the latter, cheapness of the disinfectant is a great desideratum, and when only the *excretions of healthy individuals* are to be considered, a deodorant action is sufficient.

Sulphate of iron meets these two indications. Being a metallic salt, it does not penetrate at all readily, and must consequently be frequently applied. It acts by combining with the NH_3 and H_2S.

Where it is necessary to have good penetration, quicklime deserves the preference. It is made into a paste with water. Crude carbolic acid is cheap and efficient if its smell is not too great a drawback. The latter precludes its use for the disinfection of vessels and rooms. Naphthalin is well suited to urinals, since it is so sparingly soluble and very cheap. (Also used to kill moths and other insects.)

For infected excreta, everything considered, *chlorinated lime* deserves preference. About 6 ozs. of this are mixed with a gallon of water, and a quart of this used with each discharge and allowed to stand an hour. The cresols (1 : 100) or formaldehyd (10% of commercial) are also practical and efficient. Sputa and similar discharges are best received in paper cups or napkins, and burned.

For the disinfection of the **hands, walls of rooms, articles not injured by wet,** etc., mercuric chlorid (1 : 1,000) is almost universally applicable. Its only drawback lies in its toxicity. Where this is a serious objection it may be replaced by phenol (2 : 100) or formaldehyd (4% absolute = 10% commercial). These may also be used for *instruments* the metal of which is injured by mercury. Another popular method is to boil the instruments in 1% sodium carbonate for half an hour. For *glassware,* dry heat of about 150° C., continued for an hour, deserves preference. The *bedclothing* and *dresses* of patient and nurse should be sterilized by steam, or at least by prolonged boiling. *Wool* which will not bear damp, can only be satisfactorily sterilized in special apparatus by dry heat of 110° C., or by formaldehyd gas.

Rooms.—The sponging of rooms and furniture with antiseptic solutions is never sufficient for their sterilization; for there are always many crevices which would escape in such treatment. Some method of fumigation is necessary, and the choice rests mainly between SO_2 and formaldehyd. SO_2 destroys bacteria, but not spores; it is also objectionable since it causes bleaching of all organic dyes. It is generated by burning 3 lbs. of *sulphur* for each 1,000 cubic feet of space. To avoid danger of fire, the sulphur is placed in tin pans raised from the floor by bricks. Its action is materially greater when the air is saturated with moisture.

Against mosquitoes the SO_2 is more effective than formaldehyd. It should therefor be preferred against malaria, filaria, yellow fever, etc. *Formaldehyd* is much more efficient against bacteria. For the purpose of disinfecting rooms, it is best made by burning methyl (wood) alcohol in a special lamp or by vaporizing paraform. Whilst formaldehyd is very volatile, it decomposes quite largely if it is attempted to vaporize its solution by heat, and much is lost. However, 150 c. c. of the commercial 40% solution, when vaporized, will disinfect a room of 1,000 cubic feet in ten hours. Or a number of sheets saturated with the solution may be suspended in the room.

With all fumigation the room is best kept closed over-night, then thoroughly aired, and then sponged, first with an antiseptic solution, then with water. The wall-paper in particular should be thoroughly cleaned. Where possible, a coat of whitewash should be applied, since this constitutes an efficient germicide.

In **operative technic** for open wounds the objects are to avoid local irritant action and general poisoning from absorption, and, if the wound is infected, to obtain the greatest penetration. When the wound is not infected, asepsis rather than antisepsis should be the aim. When the latter is required, preference should be given to cresol (½ : 100) or to carbolic acid (2 : 100) for penetration, and to $HgCl_2$ for local action (1 : 5,000 to 2,000). It must be remembered that these chemicals are irritant and capable of absorption. The tendency of $HgCl_2$ to form insoluble combinations with the constituents of the tissues can be greatly lessened and the keeping qualities improved by the addition of HCl, tartaric acid, NaCl, or NH_4Cl, in amount about equal to the $HgCl_2$. Hydrogen peroxid solution is used especially on suppurating surfaces. The foam which arises when it comes into contact with decomposing matter supports its action mechanically by dislodging fixed particles of bacteria, dirt, etc.

The local irritant effects are by no means always objectionable; thus, carbolic acid is sometimes used for its caustic action. On account of the anesthesia which it induces, it is very much less painful than other acids; but it is also less efficient. It is sometimes injected in strong solution into cysts to cause adhesive inflammation. Salicylic acid also has a decided caustic action, which determines its use in hyperidrosis, and for softening corns.

The irritation is an objection not only at the place of application, but also at the seat of excretion,—*i. e.,* kidneys—and nephritis constitutes a contraindication to the use of absorbable antiseptics.

The endeavor to prevent symptoms of general poisoning when a purely local effect is required has led to the use of almost insoluble antiseptics as **dusting-powders.** Many of these are also useful in promoting healing by their irritant action; on account of their slight solubility this is always mild and kept within physiologic limits. A mild irritant action of this kind stimulates cell division and, consequently, healing. The most important dusting-powders are iodoform and its substitutes, the insoluble bismuth salts, and boric acid (see Index).

The Skin.—Germicides may be useful in this situation in aiding the healing of *sores and ulcers,* or to effect the cure of *more diffuse* skin diseases depending upon the presence of bacteria or other parasites. In either case, a *mild stimulant action* seems to be quite as essential in determining the success of the remedy as the germicidal action. On the other hand, the irritant action must not be too strong. To prevent the maceration of the epidermis, the drugs must be used either as powder or in the form of *ointments.* The latter render the drug capable of absorption, and this prevents the use of any very toxic substance.

The following are the most employed: Carbolic acid, 5% ointment. Ichthyol, 10 to 50% ointment. This exerts a peculiarly beneficent irritant action, which also leads to the absorption of inflammatory swellings, etc. Tar, 10 to 100%. Resorcin, 5 to 20%. Same action as phenol and no advantage. Naphthalin and naphthol, 5 to 10% ointment. Sulphur, 10%. Pyrogallol (5 to 20%), mainly as irritant, but too dangerous if absorbed, and best replaced by chrysarobin.

The metallic salts and oxids which come under this heading will be considered under astringents (see Index).

Mucous Membranes.— The disinfection of mucous membranes requires antiseptics of low toxicity, since the absorption is comparatively great. In inflamed conditions, an astringent action is also often desirable. The most useful ingredients are the salts of zinc and boric acid. The remedies are applied to the oral cavity in the form of gargles, to the eye as eye water, and to the urethra and vagina as injections. *Gargles* are generally flavored with mint or gaultheria water, or with thymol. Ferric chlorid or alum, which are often added to gargles, act mainly as astringents. Eucalyptol and menthol are used especially in the nasal cavities.

Urinary Antiseptics.— The urine and the bladder may be disinfected to a considerable degree by drugs administered through the mouth. The antiseptics of the aromatic series are sufficiently concentrated, in the course of their excretion, to be effective, *e. g.*, in gonorrhea. Sodium salicylate or benzoate or salol are used for this purpose, as also copaiba, cubeba, sandal-wood, etc. Certain other substances are not themselves antiseptic, but are decomposed into antiseptic compounds in the course of excretion through the kidney, especially in the presence of bacteria. Arbutin, a glucosid occurring in uva ursi, and chimaphila, belongs to this class. It yields hydrochinon. The most useful product, however, is urotropin (see Index), which yields formaldehyd. This is used in pyelitis, inflamed bladder, and for rendering the urine aseptic (as in typhoid fever). Increased acidity of the urine also destroys bacteria. Dilute mineral acids, or acid sodium phosphate, may be used.

Intestinal Antiseptics.— The disinfection of the alimentary canal would be useful in various dyspepsias, intestinal putrefaction, in typhoid fever, cholera, etc. Many experiments have been directed to this end. As a result, it may be concluded that *complete asepsis is impossible* in this situation.

This is easily comprehended if one stops to consider the large number of bacteria present; the large mass of material in the intestine, tending to weaken the antiseptic and to prevent its access; the ready absorption and consequent danger of general poisoning; the sensitiveness of the intestinal canal to irritating agencies; the fact that ferment action is diminished by all antiseptics, etc.

When the antiseptics are used in such an amount as to injure the mucosa, they may even increase the number of bacteria. It was also argued, at one time, that antiseptics would be injurious by checking the saprophytic bacteria, which were supposed to be necessary for digestion. This theory has been disproved; nor do they appear to hinder the digestive ferments materially.[1]

Although a complete intestinal asepsis is an impossibility, a relative asepsis, a limitation of an abnormally increased bacterial action, is not so. This can be clearly shown by the diminution of the indoxyl and combined sulphates of the urine under appropriate treatment. Calomel may cause their entire disappearance.

The bacteria in the lumen of the intestine will be much more readily acted upon than those which have already obtained a nidus in the intestinal walls, and antiseptic measures will be of greatest benefit in the former condition.

The removal of the contents of the intestines is, of course, one of the most efficient methods, for it carries with it at once numberless bacteria and the material on which they have been nourishing. *Calomel* is the best physic for this purpose, since the slight amount of bichlorid formed from it tends to check the remaining bacteria.[1] The *bichlorid of mercury* is also used in doses of $^1/_{2000}$ grain (0.035 mg.). For antiseptics, more strictly speaking, the preference is given to those which are only sparingly soluble, so that they will not be absorbed in the upper portions of the alimentary canal. The most useful intestinal antiseptics are naphthalin, naphthol, the cresols, and guaiacol, thymol, camphor, salol, etc.

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[1] Exercise 19.

Salol is decomposed into carbolic and salicylic acid. It is only slightly acted upon in the *stomach*, and is used as coating for *pills* which are not to act in stomach. It has been suggested as a test for the length of time during which *food* remains in the stomach, by noting how much time elapses before the salicylic acid test is given by the urine. It is only of limited value, since the time varies greatly in normal individuals.

Most intestinal antiseptics act also as anthelmintics. Novy and Freer (1902) have introduced the *organic peroxids* as intestinal antiseptics. These may be considered as hydrogen peroxid, in which the hydrogen has been replaced by organic radicles. Diacetyl peroxid (acetozone) has the formula $C_2H_3O — OO — C_2H_3O$; benzoyl-acetyl-peroxids (*benzozone*) is represented as $C_7H_5O — OO — C_2H_3O$. These compounds are fairly stable, but inactive. In the presence of water, they split into acetyl-peracid ($C_2H_3O — OOH$),[2] which is more powerfully antiseptic than hydrogen peroxid, and very slightly toxic. The acetozone or benzozone are administered in capsules of 0.3 Gm. (5 grains), three times a day. They should not be mixed with organic liquids, nor kept in a warm place, as they tend to explode. The peroxid of calcium or magnesium, which liberate hydrogen peroxid in the presence of acid, have been recommended in the treatment of abnormal gastric fermentation, and as tooth powders.

Antisepsis in Tissues After Absorption.— The specific effect of quinin on malaria, of salicylates on acute rheumatism, and of mercury on syphilis, encourage the hope that other antiseptics of similar selective power may be found. So far, however, the search for these has been unsuccessful, and it may be stated as a general rule that antiseptics, when present in the circulation, kill the animal, in doses much smaller than are necessary to affect the bacteria.

Antiseptics in the Treatment of Tuberculosis.— The use of certain antiseptics, by mouth, has proven fairly successful in phthisis. The principal remedy of this class is creosote, or guaiacol; but tar, turpentine, terebene, eucalyptol, and ichthyol appear to be similarly useful. There is still some dispute as to the mechanism of their action. The theory that they destroy the toxins has been abandoned. Another theory explained their action as being local, due to their excretion by the lung. This pulmonary excretion is altogether denied for guaiacol by Bufalini (1904). Even if it does occur with some of the other drugs, it cannot be the essential cause of the action, for the sputa of the patients thus treated possess an undiminished virulence. The most satisfactory explanation is one which assumes that the action is indirect, due to a checking of intestinal putrefaction, and consequently an improved nutrition and a higher resisting power of the patient.

Not much greater success has followed the attempt to introduce these antiseptics into the lungs *via* the respiratory passages, in the form of *sprays and inhalations*. The fault lies in the fact that they do not reach the disease foci in this manner, but remain in the upper air-passages. Nor could they readily penetrate the caseous matter, even if they were brought into the alveoli. They are in consequence useful in bronchitis and bronchial pneumonia, but not in tuberculosis.

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[1] Exercise 31–2.

[2] The acetyl benzoyl peroxid decomposes into acetyl peracid, acetic acid, and the insoluble dibenzoyl peroxid, according to the equation $2C_6H_5CO.OO.COCH_3 + H_2O = C_6H_5CO.OO.COC_6H_5 + CH_3CO_2H + CH_3CO.OOH$.

Landerer has seen good effect, in early cases, from the hypodermic and intravenous injection of balsam of Peru and its main constituent, *cinnamic acid,* and its sodium salt, *Hetol.* No marked germicidal quality is claimed for them, but the causation of a *specific inflammation* of the diseased areas with consequent cicatrization. Most observers pronounce themselves unfavorably. Others concede some benefit in "walking cases," but urge the great inconvenience against the treatment: Intravenous injections must be given daily for one and one-half years. Even injurious results have been reported from its use in severe cases.

The medicinal treatment of advanced phthisis is still generally disappointing. The greatest benefits are obtained from climate, out-door life, and forced nutrition (supported by codliver oil and creosote).

When tuberculosis is located in more accessible situations — joints, skin, etc.— the outlook is more promising. *Peruvian balsam* appears to be markedly beneficent here also. *Iodoform* has been much used, either as powder or as a suspension (iodoform 10, alcohol and glycerin āā 45).

In the treatment of lupus, good results have been obtained with *Thiosinamin,* a derivative of oil of mustard (see Index). It is given by mouth in capsules (0.03 to 0.2 Gm.), or as hypodermic injection in 15 to 20% solution in alcohol. It seems immaterial whether the injections are made at the site of the disease or at a distance.

The peculiar irritation produced by the actinic rays of the sun or of electric light (Finsen treatment), of Roentgen rays, and of radium, has also proven successful with lupus and epithelioma. Their action is not understood.

CHAPTER XVIII.

TOXINS AND ANTITOXINS.

The study of these substances is not usually placed in the domain of pharmacology, but in that of bacteriology and pathology. Their description is generally found in text-books on these subjects; whilst their effects are described in treatises on medicine and surgery. This arrangement is purely one of expediency. In a sense, the actions of toxins are strictly pharmacologic; whilst the therapeutic use of antitoxins and similar substances make their discussion in this place absolutely necessary. As regards the toxins, only a broad sketch of the general principles can be given, without entering into details, and with the omission of the experimental evidence.

The Nature of Toxins and Antitoxins.— The resemblance between the effects of toxins and those of ordinary poisons is so close, that it is often impossible to differentiate, from the symptoms alone, a case of traumatic tetanus from one of strychnin poisoning, or Asiatic cholera from arsenical intoxication. The resemblance, however, is probably only superficial. A closer study of toxin-action reveals peculiarities, which serve to define these poisons into a special group. In the first place, the symptoms never develop promptly after the introduction, no matter how large the dose: a *period of incubation,* variable, but fairly definite for each toxin, always intervenes. The principal characteristic of the group, however, is that *they give rise to protective substances,* when they are injected into living animals in non-fatal doses. These so-called *antitoxins* combine with the toxin to render it inactive; they are specific, *i. e.,* they act as a rule only on the toxin which led to their production. This property is possessed by every toxin. It is also shown by proteids and ferments, the same principle probably being involved in all cases. It is convenient to restrict the term "toxin" to those which have a marked toxic action. Indeed, the latter is very powerful in the true toxins; they produce their effects in doses so small, that one is reminded of ferment action. *A toxin may therefore be defined as a substance of markedly toxic action, capable of leading to the production of a specific antitoxin.*

Our knowledge of the *chemical nature of toxins* is very limited. The analogy to proteids is obvious. Indeed, they all contain nitrogen, and many of them continue to give proteid reactions, in a high state of purification. It is quite possible, however, that some at least are not proteids in the ordinary sense.

The *antitoxins* also appear to be proteids. Those of diphtheria, tetanus, etc., cannot be separated from certain of the globulin of the serum, but it is impossible to say whether they are themselves globulim, or whether they simply adhere to the proteid, or whether the antitoxin action is merely a special property which the proteid acquires under certain conditions. The serum globulins can be separated by fractional precipitation with salts, *e. g.,* ammonium sulphate. The antitoxin is confined to either the euglobulin or the pseudoglobulin fractions, according to the nature of the antitoxin, and according to the animal. In the horse, for instance, the diphtheria antitoxin behaves as a pseudoglobulin; in the goat as a euglobulin.

The *activity of both toxins and antitoxins is readily destroyed* by excessive heat, digestive ferments, or strong chemicals.

Occurrence.—The most important toxins are those produced by bacteria. In certain cases (diphtheria, tetanus) the toxin is secreted in free form into the culture medium, *i. e.,* it is found *extracellular.* Even in these cases, however, the bodies of the bacteria contain *intracellular toxins, i. e.,* toxins which are not liberated. These are specifically distinct from the soluble toxins (Vaughan). In other bacteria (cholera, typhoid, pneumococcus), the toxins are mainly intracellular, the filtered cultures being almost innocuous. Bacteria also produce other poisons, *e. g.,* the *ptomains,* which have alkaloidal properties, and whose actions resemble those of atropin, nicotin, or muscarin. These ptomains arise especially in the course of putrefaction, under suitable conditions (limited access of oxygen). They are important in causing poisoning by spoiled food; but they have nothing to do with infectious diseases.

The production of toxins is not confined to bacteria. We have seen that they are closely related to proteids, and the latter are very apt to have some toxic action on cells not accustomed to them. Even egg-white is not indifferent when injected into the circulation. The toxic action is much more pronounced with certain blood serums, snake-venom, the poison of scorpions and spiders, etc. Not all animal poisons, however, are toxins. Cantharidin, salamandrin, epinephrin, cholin, xanthin derivatives, etc., belong to different chemic classes.

Certain of the higher plants also produce very typical toxins, *e. g.*, ricin (castor oil bean); abrin (jequirity bean); and others.

The Side-Chain Theory.— The varied and complicated phenomena presented by toxins and antitoxins can be interpreted by a theory proposed by Ehrlich. Some understanding of this theory is essential for the appreciation of modern work in this field. The theory has certainly justified itself as a stimulus and guide for research, and as a plausible interpretation of facts. The principles of this theory are fairly simple; into its details we shall not attempt to enter. The student — who has not the special knowledge, and cannot give the required detailed study — is advised to assume a receptive, rather than a critical, state of mind in mastering these principles.

Protoplasm is a physico-chemical compound of peculiar complexity. It may be conceived as consisting of a substance termed *biogen*, composed of large molecules, each molecule being an aggregate of various chemic radicles, in labile combination. The structure of the benzol derivatives may serve as an illustration; from benzol, a very large number of complex compounds may be derived, by substitution of *side-chains*, whilst the structure of the benzol-ring itself is kept intact. The great capacity of biogen to enter into the most varied reactions may be attributed to the multiplicity of its side-chains. These side-chains may therefor be called *receptors*, since they serve to receive foreign molecules into the biogen. They have a very important function in the physiology of the cell, for it is through them that food is assimilated. However, they also furnish the *means by which toxins combine with the biogen*, and hence their importance in the present connection. It is a well known fact in organic chemistry that some side-chains are better adapted for introducing a given group than others. A *specificity* exists. This specificity is very conspicuous in the biogen-receptors, so that it seems probable that every substance enters the protoplasm only through a specific receptor. In their absence, no combination can take place. This explains instances of *natural* (inherent) immunity to toxins. (It is not necessary to assume that the biogen contains ready-formed receptors for every substance with which it is capable of combining; considering the labile condition of protoplasm, it is conceivable that some receptors are only formed when the need for them arises.) It will be seen that this theory supposes the action of toxins to be essentially similar to that of foods, although the effects are so very different. The combination with the food-molecules is useful to the cell; that with the toxin-molecules is harmful.

The food compounds appear to be readily broken down, so that the receptors are again liberated. The toxin-compounds, on the other hand, appear to be firm, so that the receptors are rendered permanently useless to the cell. The cell tends to counteract this damage by producing new receptors. Indeed, it tends to do so to excess, some of the receptor groups being given from the cell into the surrounding medium, *i. e.*, the serum. These *free receptors* are also capable of combining with the toxin, which is thereby "saturated," and rendered incapable of combining with the receptors of cells. These free receptors constitute the *antitoxin*. They are necessarily specific.

Ehrlich's theory, in this, its simplest form, may therefore be briefly stated as follows: Toxins produce their effects by entering into chemic combination with the biogen. This combination occurs only through the intermediation of specific side-chains, receptors. These receptors may be given off from the cells to the serum. The free receptors are also capable of combining with the toxin, thereby preventing it from combining with the attached cell-receptors. They are the antitoxin.

Almost nothing is known about the chemic nature of these receptors, or about the reactions which take place. They are generally symbolized by pictorial representations, and this is almost indispensable to the clear conception of the details. The general principles may, however, be understood without their aid. Several different types of receptors and reactions are assumed. The simplest are those of diphtheria and tetanus. In these, the receptor consists of a combining (*haptophore*) group, especially attuned to the toxin. The latter must possess two groups, haptophore and *toxophore;* for by cautious heating, by keeping, etc., the toxin may be deprived of its toxicity, whilst it is still capable of neutralizing antitoxin.

More complicated receptors are illustrated by *hemolysins.* When a little of rabbit's serum is added to the blood of a guinea pig, the corpuscles of the latter are laked. It can be readily shown that two substances are concerned in this phenomenon: one being present in the blood of the rabbit, the other in that of the guinea pig. It can also be shown that the substance in the rabbit's blood combines with the guinea pig corpuscles, even in the absence of the second substance; but does not lake until the latter is added. This (the substance existing preformed in the serum of the blood to be laked, and indeed in all sera) is therefor considered the toxic substance, and is called the toxic complement, or briefly, *complement,* also activating body, or alexin. It does not cause laking alone, because it cannot enter directly into combination with the corpuscles, but only through the intermediation of the substance present in the rabbit's serum. The latter is therefor called the *intermediary body,* or *amboceptor,* since it combines with both the cell and the complement (also the immune body). It really represents the cast-off receptors of some cells of the rabbit. This is shown by the fact that animals which do not ordinarily produce *hemolysins, i. e.,* amboceptors against the blood of a given species, do so when the blood of this species is injected. This injected blood, together with the complement always present, serves to saturate the normal receptors of certain cells. This leads to the increased production of these receptors, and the serum thereby acquires a specific hemolytic power. The complement is destroyed by heating to 50 or 60° C.; the amboceptor is not injured by this temperature. Snake-venom also contains a hemolytic amboceptor; and Kyes has shown that in this case lecithin may act the part of complement. This injection of other cells also leads to the production of sera more or less specifically destructive to these cells (*cytotoxins*), by an essentially similar process. As a rule, these are most powerful when produced by the cells of a foreign species (hetero-cytotoxins); although they may also be produced by those of the same species (iso-cytotoxins). It is improbable that they can be caused by the cells of the same animal (auto-cytotoxins).

Welch invokes an analogous mechanism to explain the action of bacteria which do not produce demonstrable toxins (such as typhoid). He assumes that these bacteria also contain receptors, which are saturated by the receptors of the tissue cells; that in response to this, the bacteria and the tissue cells both are obliged to produce more receptors; the victory belonging to whichever can produce the receptors most rapidly. The injection of hemolysins also leads to the production of antibodies, this time to such as prevent the effect of the hemolysin. These may be either anticomplements (saturating the complement); or antiamboceptors (saturating the amboceptor).

The injection of proteids produces substances which precipitate this particular proteid (precipitin); the injection of bacteria, those which agglutinate bacteria, etc., etc. All these phenomena are covered by modifications of the original Ehrlich theory; but it would be unprofitable to follow this into further detail in this place.

IMMUNIZATION THERAPY.

Immunity, the power of an organism to resist the action of toxins, may be natural or acquired. *Natural immunity* is generally explained by the absence of suitable receptors. The serum of such animals is not antitoxic. *Acquired immunity* may be active or passive. In *active immunity* the animal is caused to produce antitoxin by the stimulus of sublethal doses of the toxin. *Passive immunity* is conferred by the introduction of ready-formed antitoxin from an actively immunized animal. Passive immunization is less dangerous and more prompt; but it is also less certain and less lasting. Moreover, the number of infections against which passive immunization is practical, is limited.

Active Immunization.— This is secured by the injection of very small doses or of weakened cultures of the infectious material. The attenuation is obtained by growth on unfavorable culture media; at unfavorable temperature (cholera); by chemicals; by heat (typhoid, plague); by drying (rabies); or by passage through certain animals (vaccinia). In most diseases the treatment has only a prophylactic value. In the case of the slowly developing rabies, it may be curative. The value in this disease, and that of vaccination against smallpox, is firmly established. The others are still in the experimental stage.

They are administered as follows:

Rabies.— *Pasteur Treatment.*— Subcutaneous injection of emulsions of the dried spinal cord of rabbits killed by rabies; beginning with cords dried for fourteen days, and advancing to those dried for three days. The simple method (for mild cases) requires sixteen days, the intensive method (for severe cases) twenty days. The treatment is of no value when symptoms have appeared.

Typhoid.— *Wright and Semple Method.*— Sterilized emulsion of dead typhoid bacilli. Hypodermic injection in doses ½ to 1½ c. c. Produces some fever and constitutional disturbance. Reports fairly favorable as to prophylactic value.

Cholera.— *Haffkine Method.*— Attenuated culture, followed after five days by a virulent culture. Favorable results as prophylactic.

Plague.— *Haffkine Method.*— Hypodermic injection of culture sterilized and attenuated by heat, in dose of 2 to 2.5 c. c. for adults. Favorable results as prophylactic, the effects lasting about a month.

Vaccinia.— The crusts and purulent matter from heifers inoculated with vaccinia; spread on ivory points, or preserved in glycerin. Introduced by spreading over scarified area of skin. Produces immunity against smallpox, the protection lasting four to ten years. The protection is more lasting when the inoculation is made from a human scab.

Passive Immunity — Immunizing Sera.— Passive immunity is induced by the injection of immunizing sera, *i. e.,* the serum of an animal (generally the horse) which has been rendered actively immune by the methods just described. These sera may be either *antitoxic* (neutralizing toxins), or *bactericidal* (killing the bacteria). Examples of the former are the sera against diphtheria, tetanus, snake venom, etc.; of the latter, those against the pneumococcus and streptococcus. (It must be remembered that the antitoxins, by depriving the bacteria of their means of defense, usually lead indirectly to the destruction of the bacteria.)

Conditions for the Action of Immunizing Sera.— The conspicuous success of the diphtheria antitoxin raised high hopes of the immediate and wide extension of the serum treatment to other infectious diseases. These hopes have only been moderately realized thus far. The reasons are not far to seek. It seems that the toxins, when once fixed in the cells, cannot be affected by the antitoxin, except perhaps by doses so large as to be impractical. The antitoxin prevents the effects of the toxin completely if it is injected in appropriate doses with or before the toxin; but if it is injected *after* the toxin, *every delay diminishes the chances of success.* This can be obviated, to some extent, by increasing the dose of the antitoxin, but only within certain limits. *Antitoxins should therefore be used as early as possible in the disease.* The same rule applies to bactericidal sera. It is evident that *the results of prophylactic injections are much more certain than those made after infection.* The results are generally good if the treatment is begun at once after infection. Once the symptoms have appeared, success is very doubtful in most cases. Sufficient toxin has already entered the cells at this time to be dangerous; the treatment will only stop the further production of toxin.

Diphtheria is a notable exception. In this disease, serious and characteristic symptoms occur so early, that the antitoxin can generally be used in time. With *tetanus,* a further difficulty exists in the fact that the toxin is apparently carried in the nerve sheaths, whilst the antitoxin remains in the general circulation, so that the toxin and antitoxin are not readily brought together.

With the *pneumococcus* and *streptococcus* sera still another difficulty arises, namely that there seem to be a number of varieties of these bacteria; the antitoxic sera being effective only against the particular variety by which they were produced, and which can only be recognized by the fact that it responds to the serum — a test which is evidently impractical.

There is reason to hope that these various difficulties are not insuperable. At the present time, the prophylactic value of the tetanus, snake antitoxin, and diphtheria antitoxins is fully established, as also the curative effect of the last, and under suitable conditions, of the two first. Passive immunization against other diseases is still in the experimental state.

The essential principles of the production and use of immunizing sera are well illustrated by the most important, the

DIPHTHERIA ANTITOXIN.

Production.— The antitoxin is produced by injecting horses with diphtheria toxin, *i. e.,* with filtered sterile broth cultures, beginning with very small doses, which are increased at varying intervals, according to the amount of reaction. This treatment is continued for from four to six months, until a high antitoxic power has been reached (as determined on small samples of blood, withdrawn from time to time). The horse is then bled from the external jugular vein, with strict asepsis. This can be easily done without anesthesia. Seven to twelve liters are collected in sterile bottles. As soon as the serum has separated, it is filtered through Berkefeld filters, and some antiseptic is added (carbolic acid or trikresol). The antitoxic strength is determined, and the appropriate doses are marketed in small flasks, usually provided with some injection device, to obviate contamination during administration.

The antitoxic power of the serum gradually diminishes on keeping, especially at a warm temperature. To obviate this, *dried serum* has been prepared, by evaporation in vacuo at a low temperature. This is dissolved at the time of administering. Its use is somewhat inconvenient and there is some risk of contamination during solution.

Standardization.— The strength of the antitoxic sera has to be determined by testing its protective power on guinea pigs. The original *immunity unit* was ten times that quantity of antitoxin which would completely protect a 250 gram guinea pig against ten times the fatal dose of toxin; in other words, each immunity unit neutralizes a hundred fatal doses of toxin.

It was found, however, that a given serum seemed to have a different antitoxic value when tested with different samples of toxin. This was explained by Ehrlich by the assumption that the filtered broth culture contains several constituents capable of neutralizing antitoxin; and that only one of these is toxic. The proportion of toxic to non-toxic neutralizing elements varied in the several cultures, so that the neutralizing and toxic qualities would not go parallel. To obviate this uncertainty a standard serum was prepared from a certain standard toxin.

This dried serum, containing 1,700 units per gram, is supplied by the Government Testing Department of Berlin to the various producing laboratories. It is here used for determining the "*test dose*" of the toxin to be employed in the actual standardization. This is *the largest quantity of toxin which can be completely neutralized by the unit of standard antitoxin,* so that a 300 gram guinea pig will survive for four days. This toxin is then used in standardizing the serum to be tested; *the smallest quantity of serum which neutralizes a test-dose of the toxin contains one unit of antitoxin.* This new unit, which is now employed universally, is approximately equivalent to the old unit, but is more uniform. The standardization of other immunizing sera has not been elaborated so fully.

Administration.— All immunizing sera are inactive when taken by the alimentary canal. They are therefore injected, with strict asepsis, into the loose subcutaneous tissue of the back or flank. Special sterilizable syringes and rather large needles must be used for this purpose. A tube of antitoxin once opened, should not be employed again.

Dosage.— The quantity of antitoxin to be used in each case depends upon circumstances. It is smaller in mild cases and when given early. The usual doses are: 200 to 500 units for immunizing; 2,000 units for mild cases; 3,000 for moderately severe cases; and 4,000 for severe cases. Larger doses are often used, to 10,000 units. The same quantity is used in children as in adults. The doses are repeated two or three times, at intervals of twelve hours, according to the progress of the case. If there is no improvement after three days' treatment, it is useless to continue.

The antitoxins on the market generally contain 500 units per c. c. For a dose of 2,000 units, an injection of 4 c. c. is required, etc. The antitoxin is now dispensed in containers of 1,000, 2,000, 3,000, and 4,000 units.

Accidents.— The injection of the serum leads to the appearance of an erythematous rash and to a slight hyperpyrexia, in about a third of the cases; more rarely to joint-pains. These effects occur about the second week after the injection. Similar actions are produced by all other immunizing sera, and even by normal serum, so that they are not due to the antitoxin. In fact, the injection of any foreign serum is more or less toxic. Horses' serum has the lowest toxicity for man, and it is this fact which has led to the choice of this animal, in addition to the large amount of serum which can be obtained. The occasional ill effects cannot be avoided at present; but they are not a serious inconvenience. Rarely, however, much more serious phenomena arise, viz., prompt collapse, which may be fatal. It is probable that the injection in these cases was made into a vein, which must be carefully avoided.

It has also been claimed that the antitoxin increases the occurrence of nephritis and paralysis. For this there is no evidence. The apparent increase may be explained by the fact that the severe cases, in which these complications are most frequent, die without the antitoxins, whilst they are saved when antitoxin is used.

Since the ill effects increase with the quantity of serum injected, it is advisable to use sera of high potency.

Therapeutic Effects.— The mortality of diphtheria is reduced by about a third when antitoxin is used. The exudation ceases spreading and clears more rapidly; it rarely extends to the larynx; the swelling of the cervical glands subsides; the fever falls promptly, and the general condition improves quickly. The occurrence of paralysis is not affected.

The very much superior results of *early administration* make it incumbent to employ the antitoxin just as soon as a well-founded suspicion of diphtheria exists; *i. e.,* without waiting for a positive diagnosis. The possible dangers of the treatment are so slight as to be negligible in view of its great benefits. It is even advisable to employ immunizing doses in case of exposure, before the disease develops.

Serum Antidiphthericum (U. S. P.).—" A fluid separated from the coagulated blood of a horse, immunized through the inoculation of diphtheritic toxin. It should be kept in sealed glass containers, in a dark place, at temperatures between 4.5 and 15° C." Sp. G.: 1.025 to 1.040. Loses 10 to 30% of its power in one year. The standard of strength should be that established by the U. S. Marine Hospital Service. Average Dose: 3,000 units; immunizing dose: 500 units (U. S. P.).

OTHER IMMUNIZING SERA.

The general facts concerning these sera have been discussed in the preceding section, and need not be repeated.

Tetanus Antitoxin.— Produced from horses; antitoxic, not directly bactericidal. The dose of the dried serum is 5 Gm.; of fluid serum, 10 to 20 c. c. The injections are repeated according to the progress of the case. The prophylactic results seem to be excellent, especially when the injections are made about the wound. After the symptoms have developed, the effects are practically negative. According to Meyer and Ransom (1903), the results are better when subdural injections are used, or injections into the nerve-trunk.

Antivenomous Serum.— Generally produced from horses, immunized with cobra venom. Calmetta's serum contains 2,000 units, *i. e.,* 1 c. c. protects 2,000 grams of rabbit against the just fatal dose. The dose is 10 to 30 c. c., injected as soon as possible, preferably by a vein. The results are favorable, if used promptly, and it appears to be effective against all varieties of snake venom.

Antipneumococcic Serum.— From horses or donkeys, inoculated with virulent cultures. 1 c. c. of Pane's serum, No. 1, protects the rabbit against 1,000 fatal doses, No. 2 against 3,000 fatal doses. Bactericidal. Dose, 10 to 20 c. c., twice a day, subcutaneously, until convalescence. Results uncertain, on account of differences in the bacteria.

Antistreptococcic Serum.— Bactericidal. Production and results as in the last. Dose uncertain. A polyvalent serum (prepared from several strains of bacteria) is recommended early in puerperal fever.

Plague Serum.— Bactericidal and antitoxic. From horses by inoculation with living cultures. Dose, 10 to 20 c. c., subcutaneously, two or three times on first day, once a day subsequently. Curative results doubtful. Prophylactic good, but lasting only four days.

The results with *sera against typhoid, cholera, tuberculosis and rabies* have been so unsatisfactory, thus far, that they require no further discussion.

Serum Against Hay Fever.— It is claimed by Dunbar that the catarrhal conditions known as spring fever, hay fever, etc., are caused by toxalbumins contained in the pollen of various plants, notably grasses and cereals, golden rod, rag weed and pigweed. These act only on susceptible individuals. By the injections of these toxins into animals, he has obtained sera for which he claims a considerable success in treating patients (in about 70% of the cases). The serum has been patented under the name of "Pollantin." It is supplied in liquid form and dried, and it is to be applied locally (a little of the dried serum, about the size of a lentil, snuffed into the nose) every morning and evening during the season. Further experience is needed to confirm its value.

THE ACTIONS OF TOXINS:

A common action of all toxins and similar substances is, that they lead to the production of specific anti-substances, which neutralize the toxins, agglutinate, kill or dissolve the bacteria. The production of these antibodies is not generally harmful to the invaded organism. On the other hand, the direct effects of the toxins on the tissue are uniformly deleterious. These effects are partly local, partly central. The local actions lead to inflammation, to necrosis or solution of cells, to immigration of leucocytes, to hemolysis, etc. In the case of soluble toxins, similar effects may be produced at a distance from the situs of the bacteria; *e. g.*, fatty degeneration of muscles, particularly the heart; nephritis; neuritis; solution of vascular endothelium, etc. Central effects consist in stimulation or depression of various parts of the central nervous system. The most common expression of this action is the production of fever: next come vascular changes. More pronounced selective actions are seen in tetanus, snake-bite, etc.

The actions produced by the different toxins are extremely numerous. With each toxin, however, they are fairly limited, on account of the specific affinity of the toxins for certain tissues. This determines the characteristics of the various infectious diseases. As these are sufficiently described in the treatises on medicine, they need not be discussed here.[1] A few animal and vegetable toxins are of special pharmacologic importance:

ANIMAL POISONS.

Snake Venom — Actions.[2]— The effects of snake venom are partly local, partly central. The *local effects* consist especially in an intense cellulitis at the site of the bite. This is accompanied by swelling and progresses to gangrene. The *blood* is also deeply affected. Its coagulability is altered, as with albumnoses. The red blood corpuscles are dissolved. There is considerable tendency to extravasation and thrombosis. The leucocytes sink to 25% of their normal number.

The systemic actions are nervous, and mainly central. The most conspicuous is a bulbar paralysis. There is a period of incubation (in man, of about four hours' duration); the patient then becomes drowsy, and then presents an ascending paralysis of the cord — *i. e.,* in the order of legs, arms, larynx, and tongue. This may be preceded by convulsive movements. There is also salivation and vomiting. The respiration becomes dyspneic, giving rise to asphyxial convulsions and forming the cause of death. The heart beats for some time after the respiration stops. A paralysis of the vasomotor center is frequent with these poisons, leading to a fall of blood pressure. The latter is in part due to peripheral effects on the heart and on the endings of the splanchnics. In the heart the paralysis involves both ganglia and muscle. There is also some curare action.

These actions are common to all snake venoms; with certain snakes, however, the local actions predominate, with others the systemic.

The fact that antivenin is effective against every form of snake bite also shows that the toxins of all snakes are essentially identical. The local and systemic effects, however, are due to separate toxins; accordingly, the bite of some snakes causes mainly local symptoms, that of others systemic effects. The hemolytic toxin is an amboceptor. Kyes has shown that the lecithin of the blood is its complement.

Treatment of Snake Bite.— The active and passive immunization has been discussed on page 395. The treatment must be very prompt. The wound should be ligated, expressed, excised or cauterized. Crystals of potassium permanganate should be rubbed in, or a solution of this, of chlorinated lime or of iodin, should be freely injected into or about the wound. Medullary stimulants, and large doses of strychnin, are useful. The popular treatment with large doses of alcohol is empirical.

Certain **lizards** (Gila monster) secrete poisons having a close resemblance to that of snakes.

Certain **poisonous fish** have glands analogous to those of snakes, and the poison from these produces a similar cellulitis. Most instances of fish poisoning are due, however, to the eating of their spoiled meat.

Scorpions contain glands on the abdomen which secrete a poison which may have an action similar to that of snake venom. Artificial immunity may be acquired by the use of gradually increasing doses, and this protects even against the local reaction.

Bees, wasps, hornets, mosquitos, and **ants** secrete a poison which produces a local irritation. This contains formic acid, but the nature of the active substances, probably toxalbumins, is not known. One of the most efficient antidotes to insect-poisoning is the local injection of a weak solution of ammonia water.

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[1] A study of the infections from the pharmacologic standpoint will be found in the first edition of this work, on pages 391 to 410.

[2] Snake venoms have no effect on infusoria, bacteria, or on plants, but they are toxic to all animals above the hydra.

Spiders secrete two poisons from separate glands. One has a local irritant action, the other is a toxalbumin and possesses systemic actions. These consist in trembling, fast pulse, cold sweat, nausea, and vomiting. The effect is rarely, if ever, fatal. A hemolytic toxin is present (Kobert, 1902).

The skin glands of the **toad** secrete a neutral poison, which is not a toxin, however. It has a digitalis action. There is also a hemolysin (Faust, 1902).

The skin of the **fire salamander** (salamandra maculata) secretes alkaloidal poisons which have a local irritant and a strychnin action, and if injected, produce death by respiratory paralysis (Faust, 1899).

Cantharidin, another animal poison which is not a toxin, is discussed in another place. A similar poison is secreted by many caterpillars.

The bodies of *tapeworms* contain a globulin-poison whose actions resemble the albumoses. It produces hemolysis, positive chematoxis, paresis, clonic convulsions, etc. *Anchylostoma* contains an anticoagulant substance. It is possible that the severe anemias which are often associated with intestinal parasites may be due to the production of toxins.

The cervical glands of the common **leech** (Hirudo) secrete a substance (hirudin, hemophilin) which delays or hinders the coagulation of blood, inside and outside of the body. This substance is not destroyed by boiling or by alcohol. It appears to be a deuteroalbumose.

Therapeutic Use.— Leeches were at one time used extensively for the abstraction of blood in local inflammations. Dry or wet cupping is now usually substituted, but they are still employed occasionally; two to four of the animals are applied. The skin should be well cleaned, and, if necessary, a little milk should be rubbed on, to tempt the animals to bite. They should not be removed, but allowed to fall off. They cannot, of course, be used again. It is sometimes difficult to stop the bleeding.

TOXIC ACTION OF PROTEIDS.

Probably every proteid is to some extent injurious when injected directly into the circulation. The degree of toxicity varies greatly, however.

Cytolysins.— It will also be remembered that the injection of emulsions of the cells of one animal into another causes the latter to produce substances which destroy the cells originally injected; *e. g.*, the injection of an emulsion of the kidney cells of a dog into the rabbit gives to the blood of this rabbit the property of causing necrosis of the renal cells when injected into dogs. Other gland cells are also affected by the serum, but to a lesser degree. These cytolysins are called *heterolysins* when they are produced by the injection of cells from another species, as in the instance given. Cells from the same species may also give rise to cytolysins, which are then termed isolysins. It may be doubted whether it has been demonstrated that an animal can produce cytolysins (autolysins) from its own tissues.

Blood Serum.— The injection of the blood serum of certain animals into other species causes severe effects, especially when the injection is made rapidly. (The more mild effects were described on page 394.) The symptoms of the severe action consist particularly in fever, fall of blood pressure, general convulsions with opisthotomos, dyspnea, paralysis, myosis, and coma. Nephritis is frequent. Hemolysis is a common effect. It is produced by toxins (amboceptors).

The most toxic of all sera appears to be that of the eel.

Albumoses and Peptones.— The intravenous injection of these substances causes fever, and a considerable *fall of blood pressure*, due to vasomotor paralysis, especially of the splanchnic area. It is still under discussion whether this action is central or peripheral. The *secretions* — and particularly the lymph — are *increased*, perhaps by this vasodilatation.

The albumoses have a peculiar effect upon the *coagulability of the blood*. Very small and very large doses hasten the coagulation, whilst ordinary doses *retard* it in most animals. The effect is not seen on shed blood, but appears to be due to the stimulation, by the albumose, of the production of substances favoring coagulation. The liver seems to be necessary for this process.

It has been claimed that these actions of albumoses are due to the presence of foreign toxins; but the most recent work (Underhill, 1903) again refers the toxicity to the proteoses themselves. *Protamins, histones*, etc., seem to have similar actions (Thompson, 1900).

TOXINS OF HIGHER PLANTS — PHYTOTOXINS.

Typical toxins occur in the castor oil bean (ricin); jequirity bean (abrin); croton bean (crotin), and in others. The three which have been named are the most important. They resemble each other very closely in action, and are *very powerful*, crotin being the weakest. Their administration leads to the production of *antitoxins*, so that an immunized animal can survive 5,000 ordinary fatal doses of ricin. (The agglutinating reaction of the red blood corpuscles is not lost in immunization.)

No ricin or crotin is present in castor oil or croton oil. There is still some discussion as to whether these toxins are true proteids. The most recent work seems to show that they are, for a preparation of ricin has been obtained, which is a typical albumin, and which is so active that 0.0005 mg. is fatal to a kilogram of rabbit; *i. e.*, one part of the ricin is fatal to 2,000,000 parts of rabbit; the fatal dose for man would therefore be about 0.035 mg. or $^1/_{2000}$ grain (Osborne, Mendel, and Harris, 1905). The agglutinating action is also very powerful. Frogs have a much higher resistance, but this is lessened by raising their temperature. Ricin is digested by trypsin; it is excreted by the intestine.

Ricin is the most important of the phytotoxins. The eating of castor beans has repeatedly caused poisoning; three or four beans may cause violent gastroenteritis, with nausea, headache, vomiting, colic, bloody diarrhea, thirst, emaciation, and great debility. The symptoms usually do not set in until after several days. More severe intoxications cause small frequent pulse, cold sweat, icterus, and convulsions. Death occurs from the convulsions or from exhaustion. The fatality is about 6%. This small fatality is due to the destruction of the poison in the stomach. The actions can be best studied on rabbits, by hypodermic or intravenous injections. They are partly local — gastroenteritis; and partly central — paralysis of the respiratory and vasomotor centers. The local inflammation also occurs on other mucous membranes to which the poison may be applied, especially the conjunctiva. (The phytotoxins have no effect on isolated muscle-nerve preparation.

The *autopsy* findings are very characteristic. They consist in swelling and reddening of Peyer's Patches, internal hemorrhages, and swelling of the retroperitoneal lymph glands. The site of the injection is boggy.

Outside of the body, ricin causes *agglutination of the red blood corpuscles* of all animals. This action does not seem to occur within the body.

Abrin, a toxalbumin from Jequirity bean, resembles ricin so closely in its action that the difference was only established when it was noticed that immunity against one did not constitute immunity against the other. When the whole beans are swallowed, no toxic effects result, since the shell is so hard that the poison does not dissolve. But if the powder is taken, it produces effects similar to ricin. The action on the eye is much stronger, causing ophthalmitis. This is sometimes utilized therapeutically, but is not justifiable, since it is impossible to control the action. This inconvenience has recently been overcome by employing standardized solutions and checking the action with an antitoxic serum.

* **Abrus precatorius.**— *Jequirity Bean, Prayer Bean.*— Papilionaceæ; tropics. An infusion may be made by macerating the powder with 50 parts of cold water.

Phallin and Helvella-acid.— These are toxalbumins contained in Helvella esculenta, Amanita phalloides, and other mushrooms.

Their action consists especially in a very marked solvent power on red blood-corpuscles, similar to that produced by saponins, but occurring inside the body. This results in extravasation of blood, dissolution, and a number of similar actions. Some of their effects are also primary. The symptoms show a close analogy to yellow atrophy of the liver. These symptoms appear only after hours, or sometimes after days. They consist in gastro-enteritis, cold sweat, somnolence, headache, delirium, coma, convulsions, cyanosis, fever, hemoglobinuria, and albuminuria or anuria.

These poisons are destroyed by drying, or may be removed by hot water, so that these mushrooms may be eaten with impunity after this treatment.

TUBERCULIN.

This intracellular bacterial toxin has some therapeutic interest. The original tuberculin of Koch is a sterile glycerin extract of the bodies of tubercle bacilli. Its injection has no effect on normal animals; but even very minute doses cause an intense reaction in tuberculous animals. This is shown by the production of fever, and by acute inflammatory changes about the nodules. This may lead to the conversion of the nodule into fibrous tissue, and may thus effect a cure; on the other hand, it may cause necrosis, and lead to a further dissemination of the tuberculous process. It may be of benefit in lupus and in tubercular joints. For this purpose, gradually increasing doses are injected hypodermically into the back. It is well to begin with $^1/_{1000}$ c. c., increasing by $^1/_{1000}$ c. c. until $^1/_{200}$ c. c. is reached; it is then increased by $^1/_{500}$ c. c. until $^1/_{100}$ c. c. is reached. Larger additions may then be made. The total dose should not exceed $^1/_{10}$ c. c. as a rule. The dilutions are made with 0.5% carbolic acid. In pulmonary tuberculosis its use is distinctly dangerous. It should be remembered that it has no direct effect on the bacilli.

The greatest value of tuberculin is as a means of diagnosis. A rise of temperature of 1° F. is taken as the index of the reaction. The injection should be made between 6 and 8 P. M.; and the temperature on the next day taken every three hours. (The normal temperature should be ascertained for two days previously.) The first injection

* Not official.

should be $^1/_{1000}$ c. c. for adults, $^1/_{3000}$ to $^1/_{2000}$ c. c. for children. If there is no reaction, another injection of $^1/_{200}$ c. c. (for children $^1/_{3000}$ to $^1/_{1000}$ c. c.) is made; and if necessary a third injection of $^1/_{100}$ c. c. (for children $^1/_{1000}$ to $^1/_{200}$). When given in this guarded manner, there is practically no danger. A positive reaction is not quite distinctive, since it is sometimes seen in other affections. The test is also widely used for the detection of tuberculous cattle. Another form of the tuberculin (Tuberculin R) has been prepared by the extraction of cultures grown on solid media. It is somewhat milder, but no more successful; and it has been found to contain living bacilli, so that its use should be condemned.

CHAPTER XIX.

THE SERIES OF HYDROCARBON NARCOTICS.

ALCOHOL, GENERAL ANESTHETICS HYPNOTICS, FORMALDEHYD.

(A) GENERAL.

I. INFLUENCE OF CHEMIC STRUCTURE ON ACTION.

This series includes all such hydrocarbon compounds — derivatives of the fatty series CnH_2n+_2 — in which the hydrocarbon portion is the active part. In order that they may exert their specific pharmacologic action, it is necessary that they be capable of absorption and distribution in the liquids and tissues of the body. This may be either by direct solution, as in the case of chloral; or, in virtue of their volatility, as with chloroform. Members of the series which are neither soluble nor volatile — such as paraffin — have no action. There is reason to believe that the physiological action depends on a solution of the fatty constituents (lecithin and cholesterin) within the cells. This is determined by the *solubility coefficient,* viz., the solubility in oils divided by the solubility in water. This factor, and therefor the physiologic action, varies in a definite manner with changes in the chemic composition.

The influence of chemic structure upon the action has been very fully studied in this series. The following conclusions appear justified: Other things being equal, the strength of action increases with the length of the chain; the greater the value of *n*, the stronger will be the action.[1] A limit is soon reached, however, for the drugs become less volatile and less soluble the higher they stand in the series; so that the higher paraffins are entirely insoluble and inactive. The ethyl radicle, C_2H_5, seems to be best adapted to therapeutic purposes. The action may be modified by replacing the H of the group by other ele-

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[1] The boiling-point and the relative toxicity of the alcohols are given as follows:

	Boiling-Point.	Toxicity (Baer).
Methyl, CH_3OH, ...	65.0	0.8
Ethyl, C_2H_5OH, ...	78.5	1.0
Propyl, C_3H_7OH, ...	98.0	2.0
Butyl, C_4H_9OH, ...	107.0	3.0
Amyl, $C_5H_{11}OH$, ...	131.0	4.0

ments or groups. The compounds so formed all possess the typical action of the hydrocarbon group; but this may be so overshadowed by other actions as to be scarcely appreciable. A good example of this is the introduction of the group NO_2. This acts very much more strongly than the hydrocarbon part of the molecule, and consequently the nitrite action is obtained long before there can be any hydrocarbon action. The same is true if we substitute an aromatic radicle. The introduction of certain other radicles weakens the hydrocarbon action to a very great extent. We may mention especially the acid-forming radicle CO_2H. The introduction of hydrocarbon radicles into an amin molecule destroys their action entirely. The introduction of more than one OH group also weakens or destroys the action. Aldehyds and ketones are more active than the corresponding alcohols. The introduction of the halogens, and especially of Cl, often enhances the action, but this is not proportional to the number Cl molecules introduced. The introduction of O (ethers) also increases the action. The introduction of acids (esters) weakens it.

II. THEORIES OF THE ACTION OF HYDROCARBON NARCOTICS.

Alcohol and the members of this group are amongst the very few drugs with which it has been attempted to reach the real explanation of the phenomena, and to go behind the bare statement that they act stimulatingly or depressingly on such and such structures. A number of hypotheses have been advanced, but the question cannot be considered as conclusively answered.

In the first place, it was suggested that these narcotics *rendered the blood incapable of nourishing the brain,* in some mysterious manner. But since chloroform acts upon a frog whose brain has previously been deprived of all nourishment by replacing its blood with normal salt solution, this theory cannot stand. The same objection holds against the theory that the narcosis is produced by insufficient nourishment of the brain through *disturbances in its circulation.* Nor are all observers agreed on just what these changes are; they must be looked upon as incidental rather than causative. They are due probably to the effects of alcohol on the circulation elsewhere — the dilatation of the splanchnic and cutaneous vessels, etc. It must be considered as proved that these narcotics act directly upon the nerve-cells. In regard to this, there are three main theories, two based upon chemic, the other upon histologic, evidence.

Claude Bernard was inclined to refer the action to a semi-*coagulation of the protoplasm,* but his view was based solely on analogies. *Binz* showed histologically that the cells of fresh brain sections are coagulated by solutions of chloroform or morphin; but he had to employ relatively enormous concentrations, nor could it be supposed that the coagulated cells could ever resume their activity. None of these theories are therefore satisfactory.

Meyer and *Overton* independently discovered the fact that the anesthetic action is proportional to the *coefficient of solubility, i. e.,* the solubility in oils, divided by the solubility in water. In other words, *the narcotic action varies with the solvent power for fats.* This forms the basis of their theory, namely, that the anesthesia is produced by a fluidification of the fatty (lipoid) constituents of the nerve-cells (especially lecithin and cholesterin), upsetting in this way the normal conditions. The action cannot be due to an actual removal of fat from the cell, nor to alterations of the permeability of the cell wall, because recovery occurs very promptly when the anesthetic is removed; direct experiments also speak against this mechanism. The theory does not apply to alkaloidal narcotics, such as morphin. *This theory, that the anesthetic action is due to a solution of the lipoids within the cell, agrees best with the facts, and may therefor be accepted.*

For instance, if the theory is correct, every absorbable substance which is a fat-solvent should have an anesthetic action; this should be seen in all cells (since every cell contains lipoids); it should occur in the same concentration of solution; the anesthetic action of a mixture should equal the simple sum of the actions of its constituents; the effect should be proportional to the concentration, and not to the absolute dose, etc. These are the actual facts. The *relation of concentration to action* is especially interesting. Precisely the same concentration of chloroform or ether produces the same degree of anesthesia in all cells (excepting plants and a few invertebrates). For instance, ordinary anesthesia required in all animals a concentration of anesthetic to serum, of ether, 1 : 400; of chloroform, 1 : 4,500 to 6,000; but cold-blooded animals reach the same concentration in the blood with a lesser concentration in the air, on account of their lower temperature.

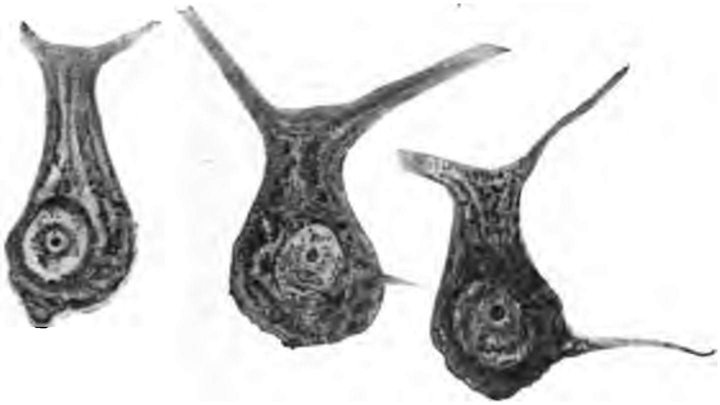

FIG. 80.— Alcohol on Purkinje cells, cat — Nissl stain (after C. C. Stewart): 1, Normal; 2, alcohol for fifty minutes; 3, for fifty-four hours.

It may well be supposed that the changes in the physical composition of the cell will produce corresponding changes in their histologic structure. Most of these would probably disappear in the process of fixation, but certain of them appear to persist. A diminution and fusion of the *Nissl granules* has been described by good observers after deep anesthesia (Fig. 80); other observers have not been able to confirm this, and the changes may be only artifacts. It is also stated that the dendrites of many pyramidal cells show moniliform enlargements; the alterations disappearing completely within forty-eight hours, even when caused by chloroform anesthesia of nine hours' duration.

III. SUMMARY OF ACTIONS.

1. A precipitation of proteids, leading to irritation and death of tissues, and hindering the action of ferments and the growth of bacteria.
2. Reflex actions resulting from this irritation.
3. A depressant (narcotic) action upon the central nervous system, exerted primarily upon the higher centers of the brain, and lastly upon the medulla.
4. A similar depressant action on all cells, and a laking of blood corpuscles; these are seen especially on local application.
5. In the case of alcohol, the capability of oxidation and consequently of acting as a food.

IV. DETAILS OF ACTION.

1. The **local action** rests largely on a coagulation of proteids, just as in the case of the aromatic antiseptics.

The cause of this coagulation differs in some respects in the various members. In the case of *alcohol* it rests upon withdrawal of water, and consequently all proteids are affected; *chloroform* has a more marked action upon globulins (especially myosin), and *ether* upon albumins (especially egg-albumen). Many of the other members of the series resemble one or the other of these three.

2. This coagulation of protoplasm causes **irritation and inflammation,**— an increase followed by diminution and finally abolition of function,— which are manifested in various ways on the administration of these substances.

When given in concentrated form, they cause a sensation of burning on the **mucous membranes** with which they come in contact. This is strongest with the aldehyds (*e. g.*, *formaldehyd,* and acrolein, the irritant vapor formed in the overheating of oils). In the *stomach* they give rise to vomiting (especially chloroform). The continued use of concentrated alcoholic liquids brings about chronic gastric catarrh, and consequently impairment of nutrition. In dilute form the changes are much less, and may even be absent.

Whilst alcohol is partly burned, much of it remains unchanged, and this holds still more of most of the other members of the series. During their **passage through the body** they cause similar irritations in other organs. These are most marked in the *liver and kidneys,* and result in inflammatory changes, especially interstitial. If the course of the poisoning is slow, as in alcohol, *connective-tissue proliferation and fatty degeneration* are the principal lesions. Chloroform and ether produce inflammation of the kidneys much more quickly than alcohol; a single administration may result in typical acute nephritis with albumin, casts, hemoglobin, etc. It is scarcely necessary to assume a special susceptibility of these organs toward the local action of the series, since they are situated respectively at the portal of entry and of exit, where the drugs are, of course, in the most concentrated form.

Smaller doses of alcohol cause *diuresis* through this irritant action.

In addition to their coagulant action, the insoluble and volatile members of the series irritate as molecular foreign bodies, since they penetrate tissues readily by virtue of their volatility, but do not mix with their constituents. On this quality rests their employment as embrocations: they produce a slight but deep irritation. When applied to the **skin,** this results in redness and a sensation of burning, which in the case of some (chloroform) becomes very *painful.* This is followed by local *anesthesia.* Alcohol in greater dilution (25% to 50%) produces an increased cell division when applied to wounds, and an increased secretion of digestive juices and more rapid absorption when taken by the stomach.

When the more volatile members are applied to the skin and allowed to evaporate, this abstracts heat, resulting in a *sensation of coolness,* in place of the burning noticed if they are rubbed in or covered. This abstraction of heat may be carried to actual freezing of the tissues by using the volatile substance in the form of spray — a method made use of for the production of local anesthesia. (See p. 226.) Some also cause stimulation of the *nerves of* **taste and smell;** the bouquet of wines and liquors is due to members of this series — for the most part unknown — and grouped together under the name "*œnanthic ethers.*"

Applied directly to a **muscle or nerve,** they act like any other protoplasmic poison, producing increase and then diminution of function. They also paralyze cilia, and in fact, all cells, animal and vegetable.

When injected near a nerve-trunk, they may cause paralysis due to a circumscribed neuritis — a fact important to bear in mind in making hypodermic injections of alcohol or ether or of alcoholic extracts.

The *conductivity of the nerve* is lowered, as well as its excitability; for if a nerve is exposed to ether vapor, stimulation at the proximal end ceases to be effectual much sooner than at the distal end. The excitability is recovered if the ether is washed off in time. With chloroform, recovery is more difficult.

The coagulating action also determines the **antiseptic properties** of this series. Their efficiency is much less than that of the aromatic group. Formaldehyde is an exception.

Iodoform owes its action, not to the hydrocarbon part of its molecule, but to the iodin liberated from it.

The hydrocarbons are also very efficient parasiticides.

They are of no great value as *anthelmintics,* since they are too rapidly absorbed and produce too great a local irritation.

3. The **action upon the central nervous system** is *purely depressant,* according to most pharmacologists. It agrees with morphin in affecting primarily the higher psychic functions, but differs from it in lowering, instead of heightening, the reflexes.

Four stages may be distinguished in this nervous action:

1. The so-called *" stimulant " stage,* when the activity of certain centers appears increased.
2. The *narcotic stage,* in which a marked lowering of the psychic functions and a disturbance of the " balance of the brain " become apparent.
3. The *anesthetic stage,* with loss of motion, of consciousness, of sensibility to pain, and of some reflexes.
4. The *paralytic stage,* with total abolition of the cerebral, spinal, and lastly of the medullary centers, the latter causing death.

This description applies to all the hydrocarbons which may be classed in this series. But great differences exist in the readiness with which one stage passes into the other. These differences are merely quantitative. Alcohol, ether, and chloroform, for instance, form a regular series in this respect. But this difference is an extremely important one practically, so that it will be better, in so far as the action on the central nervous system and the therapeutic uses are concerned, to subdivide the subject into three groups, placing alcohol in one, the general anesthetics in the next, and the hypnotics of the hydrocarbon series in the third. A fourth group is constituted by formaldehyd, which is not anesthetic, but antiseptic.

(B) THE ALCOHOL GROUP.

I. THE STIMULANT OR EXCITEMENT STAGE

is observed in most cases after taking " moderate " doses of alcohol — a quantity not easily expressed in cubic centimeters. The phenomena are only too well known. They are, at first view, typical of stimulation. There is an increase in the rate of the *respiration* and of the *heart;* the *blood pressure* rises. The *skin* is reddened, with a grateful sensation of warmth and comfort. There is an increased *vivacity* of motion, action, and speech, which latter may acquire a stamp of brilliancy, even of inspiration. The *subjective condition* of the individual also undergoes a peculiar change.

Shyness, if it ordinarily exists, is replaced by self-confidence. The person under the influence of alcohol feels an unlimited confidence in his own powers and accomplishments, both intellectual and physical. He will attempt very difficult, even impossible, tasks, and feel that he accomplishes them. And he similarly overestimates the productions of others.[1]

These manifestations are so conspicuous and apparent, that alcohol in proper doses has been considered a typical stimulant; this opinion is still held by some eminent pharmacologists. However, the experimental study of its actions tends to the conclusion that *few, if any, of these actions depend upon true direct stimulation* of the nerve-centers; but that they are the indirect result of incoordination, of accessory factors of environment, and of reflex stimulations.

If the phenomena be somewhat more closely inquired into, this will become apparent at once. Of the physical phenomena, the **flushing of the cutaneous vessels** — to which the sensation of warmth must be attributed — occurs as the result of a vasomotor paralysis, restricted, it is true, to this area. The **quickened pulse** results partly from reflexes caused by swallowing and by irritation of the mucous membranes, partly from the increased excitement and motion; not at all from a direct action on the cardiac nervous or muscular mechanism — for it is entirely absent in animals, and very brief in man if the factor of excitement be eliminated. The quickening of the respiration is also largely due to similar causes.

The increase occurs, however, even in sleep, so that the factors of environment are not essential. Nor can it be affirmed that it is due to reflex irritation, for other irritants do not produce an equivalent effect. The increase is quite large; the amount of respired air may be doubled. The effect is especially large in fatigue, and is greater with wines and liquors rich in "bouquet," than with dilutions of pure alcohol (Binz, 1903).

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[1] No better description of these effects can be given than that of Horace: "What wonders does not wine! It discloses secrets; ratifies and confirms our hopes; thrusts the coward forth to battle; eases the anxious mind of its burthen; instructs in arts. Whom has not a cheerful glass made eloquent! Whom not quite free and easy from pinching poverty!"

The **psychic phenomena** find their explanation in a dulling of certain mental faculties whilst others are still practically unaffected — in a disturbance of what has been called the "normal balance of the brain." The first functions to be lost are the finer grades of judgment, reflection, observation, and attention — the faculties which have largely been acquired through education, and which constitute the elements of the restraint and prudence which man usually imposes on his actions.

Thus, to quote a well-known example: The orator no longer considers that he may be called to account for his utterances; he allows himself to be carried by the impulse of the moment, without reflecting on ultimate consequences, and, as his expressions become freer, they acquire an appearance of warmth, of feeling, of inspiration. And not a little of this inspiration is contributed by the audience, who are usually in a similar condition of increased appreciation.

The view that alcohol increases the intellectual and physical powers of the individual is shown by actual experiment to be erroneous, and based almost entirely upon the subjective conditions of the individual, his weakened faculty of judgment.

Ergographic experiments show that moderate doses (10 Gm.) at first increase the power of voluntary muscular work (to 9%), but in one-half hour diminish it to 6% below normal. The increase is only seen when the muscle is not too much exhausted, but it is favored by moderate fatigue. The favorable effect appears to be due partly to the direct food-value of the alcohol, partly to a central action. The depression is purely central (Hellsten, 1904).

On *frog's muscle,* minute quantities have no effect; moderate doses exert a favorable action on all the features of muscular activity; larger quantities are very unfavorable (Lee and Salant, 1902).

Kraepelin, who has probably done the most extensive accurate work on the psychic effects of alcohol, states it as his opinion that the association of words and ideas is favored by it, but that the rapid association of disconnected syllables, as in psychologic experiments, is diminished. Memorization is not interfered with.

Experience soon teaches this lesson: that alcohol does not really stimulate. Persons who have to undergo severe exertion, either physical or intellectual, very rarely take alcohol before or during their labor, but only when this is finished. And then not for any stimulating, but really for its depressing, effect; for the feeling of comfort and general relaxation which it induces. The continued use of large doses of alcohol greatly diminishes the activity of the individual, and even moderate doses tend to have the same effect.

Another very characteristic feature, evidently resulting from this paralysis of the higher functions is the *loss of the power to control moods.* There may be causeless merriment or sadness, friendliness or the opposite. It is interesting to note how often alcohol brings out the true character of an individual by this abolition of restraint: "There is truth in wine." On the other hand, the habits of self-control, where they have been cultivated, persist to some extent even in intoxication.

These facts being established, it may be asked: *Why do we continue to speak of alcohol as a stimulant?* How may the undoubted benefits in general debility, in shock, in high fever, etc., be reconciled with the view that alcohol does not stimulate the central nervous system? The answer must be that the explanation is not the same in all cases, but that it is in no case necessary to assume any *direct* stimulant action. This will be discussed in the therapeutic part.

II. PARALYTIC STAGES.

The symptoms of the first stage being so largely paralytic, it is plain that no sharp line can be drawn between it and the second stage; and, similarly, there is a very gradual transition between the second and third; all the stages, in fact, being but periods in the same progressive paralytic process.

The **narcotic stage** may be said to exist when the symptoms of lessened psychic activity assume prominence. *Sensation* and *motion* become lessened. *Speech* is thick and muttering, the *gait* uncertain, the *special senses* are blunted. There is tendency to *sleep.*

Consciousness and sensation are gradually completely abolished, and this constitutes the third or **anesthetic stage.**

In the **paralytic stage** proper, the *symptoms* are those *of beginning medullary paralysis:* The *respiration* is slow and stertorous, the pulse scarcely discernible. *Skin* cold and cyanotic. *Pupils* generally dilated. *Reflexes* abolished. If very large doses have been taken on an empty stomach, these paralytic symptoms come on at once. **Fatal cases** from acute poisoning are very rare: in these the coma grows deeper and death finally results, usually from edema of the lunge or stoppage of respiration. In **subacute cases** it may occur suddenly during convalescence as a result of the gastric irritation, or from the debilitation. The fatal dose is stated as 60 to 180 Gm.

Ordinarily, however, the course is very slow, and almost always ends **in recovery.** The coma — if the intoxication has progressed so far — passes into natural sleep, and on awakening there follows a series of symptoms pointing mainly to *acute gastric catarrh,* and perhaps to neuritis; and grouped by the Germans under the name of "Katzenjammer": headache, coated tongue, loss of appetite, irritable stomach, muscular pains, etc. These show curious peculiarities for the various alcoholic liquids. The reasons for these differences are not known.

Directing more particular attention to the **effects upon the medullary centers,** a primary direct paralysis may be made out, although, as has been said this may be preceded by reflex stimulation.

The **respiration** is generally quickened through excitement; but if this is excluded, it is usually diminished (Fig. 82 *B,* p. 430).

The effects of alcohol on the **circulation** (Fig. 82 *A*) are still very obscure, notwithstanding numerous researches; they appear to vary with conditions.

In the **excised mammalian heart,** very low concentrations of alcohol (0.13 to 0.3%) are somewhat stimulant; depression appears only when the concentration exceeds 1%. Diastole is not increased. The heart recovers rapidly, even from very severe depression, when the alcohol is removed (O. Loeb, 1905).

Kochmann (1904) finds no indication of stimulation in the excised mammalian heart, by any concentration. The muscle is damaged only when 2% is reached; 4 to 5% arrest in diastole. In intact mammals, he finds some stimulation, the heart being better nourished on account of the vascular changes (1905).

The blood-pressure is scarcely altered by moderate doses of alcohol, in normal animals or in those suffering from infectious fever. There may be an insignificant rise. This negative behavior of the blood-pressure must not be interpreted as proof that there is no action on the circulation. On the contrary, Wood and Hoyt (1905) have shown by the strohmuhr that the rate of flow is considerably increased; there is also a considerable rise of pressure if the alcohol is administered after division of the spinal cord. These facts demonstrate that *alcohol produces two important effects: an increased output of the heart, and a vasodilation by depression of the vasomotor center.* These two actions largely counteract each other as regards blood-pressure: but they support each other in causing an *increased blood-flow through organs.* The cardiac stimulation tends to be further increased by the *quickened rate,* due to the excitement.

The *vasodilation* is not equally strong in different areas. The cutaneous vessels are affected most conspicuously, so that the plethysmograph shows a marked increase in the volume of the human arm. The gastric vessels are also dilated through the local irritation. The *cerebral vessels* show at first a marked constriction, followed by dilation through diminished tonus (Aliprandi and Fornaroli, 1905).

The vasodilator action of alcohol is doubtless central; its peripheral action on the vessels tends to constriction (Plumier, 1905).

Large doses of alcohol depress both the heart and the vasomotor center, so that the fall of blood-pressure is very conspicuous.

The *skin*, after severe alcoholic poisoning, may show effects resembling those of contusions or burns: edema, blisters, extravasation of blood, and gangrene. Bedsores are especially common. These effects may perhaps be due to injury to the capillaries, or neurites.

These remarks upon the action of alcohol on the circulation apply only to the normal individual. With *debilitated individuals* it may markedly raise the rate and efficiency of the heart, and consequently the blood pressure, probably mainly by acting as a food.

As a consequence of the cutaneous vasodilatation, there is a *fall in the temperature* of the body, especially when the external temperature is low. At the same time there is a sensation of warmth, and an actual rise of the temperature of the skin, through this increased cutaneous circulation.

III. EFFECTS OF ADMIXTURE OF OTHER SUBSTANCES (ETHERS, ETC.).

Before leaving the actions of alcohol on the central nervous system, some peculiarity of action possessed by the different forms of spirits may be discussed. These divergences from the typical effects are due mainly to substances other than alcohol, but for the most part not known.

It may also be remarked that the action of a given amount of alcohol varies with the concentration. The greater the alcoholic concentration of the liquid, the greater will be its local and systemic effect (the latter on account of the quicker absorption).

Beer owes its marked *hypnotic qualities* to the lupulin of the hops as well as to the alcohol. Some wines are also hypnotic, whilst others — the majority — are exalting.

The *diuretic action of* **gin** is largely due to the essential oils contained in it. Partially fermented wines produce particularly often a disturbance of the equilibrium, sometimes seen with other forms of spirit — the individual becomes "knee drunk," *i. e.*, incapable of maintaining the upright position, before the paralysis of the mental functions has progressed to a great extent. **Absinthe** produces hallucinations and finally epilepsy.

The **stronger spirits** contain, besides alcohol, substances which may pharmacologically be divided into two groups: those that give the bouquet (flavor) and have no other marked action; and those that have a deleterious effect. The latter — which are commonly called impurities — are largely destroyed by age. The most common is amyl alcohol (fusel oil).

The action of these, as far as studied, is, upon the whole, similar to that of alcohol itself, but more toxic. The ***higher ethers*** are said to be more stimulant to respiration. The *aldehyds* have a strongly irritant action on mucous membrane — as shown by formaldehyd or acrolein (allyl-aldehyd — the vapors of overheated fatty oil). The relative toxicity of the higher alcohols has already been given. The most important is *amyl alcohol,* the so-called *fusel oil.* It has a more violent acute action and more pronounced after-effect than the ethyl alcohol. But its admixture up to 1% produces very little difference in acute intoxication. *Furfurol,* which was formerly believed to modify the nature of the intoxication, does not appear to do so. But it must be said that this whole subject is much in need of thorough investigation.

The deleterious effects of higher alcohols have been studied experimentally only in acute poisoning. It is quite conceivable that their late actions may differ more markedly from those of ethyl alcohol, as they do, *f. i.,* in the case of methyl alcohol. Indeed, it must be confessed that we know very little about the action of impure spirits and wines, or about the substances which are responsible for the deleterious effects.

Artificial liquors are made by the admixture of ethers and essential oils to alcohol. Their action is not uniform, but it is generally more irritating locally, and more injurious to the brain.

Wood Alcohol.— The extensive use of this substance (*methyl alcohol*) in the arts, and its occasional fraudulent presence in alcoholic liquors, give it some toxicologic importance. The crude wood alcohol has a very repellant odor, but this is practically absent in the refined brands (Columbian Spirits). The acute toxicity of wood alcohol is less than that of ethyl alcohol, its action being weaker and the stages slower. In subacute poisoning, on the contrary, it is more toxic than grain alcohol, and produces degenerative changes in the retina leading to blindness; effects which are entirely absent in grain alcohol. It has been shown that these differences are due to the decomposition products which are formed in the body. The methyl alcohol is not completely oxidized, but is retained for a long time, being slowly excreted, in large part as formic acid. It is to this, and to the formaldehyd which probably occurs as an intermediate product, that the special toxicity is due. The effects of ordinary wood alcohol are exaggerated by the impurities (acetone, etc.) which it contains, but its toxicity is undoubtedly due in the main to its methyl-alcohol. It is stated that its consumption may also lead to a comatose condition, extending over several days. The use of methyl alcohol, except for burning, etc., in the arts, should be absolutely prohibited (R. Hunt, 1902).

IV. ACTION OF ALCOHOL ON DIGESTION.

Alcohol could be conceived as influencing the process of digestion by acting on the ferments, on secretion, on the movements of the alimentary canal, or on absorption. And, in fact, it acts in all of these ways. (All the different alcohols agree qualitatively in their action on these functions.)

(a) Action on Ferments.— Since alcohol is very readily absorbed, and no great amount of it reaches the intestine, it can only influence the ferments of the stomach, and its action on pepsin is alone of practical interest. It is found that *in vitro* — and there is no reason to suppose that it acts any differently *intra vitam* — 1% to 2% of alcohol increases the rapidity of peptic digestion. Up to 15%, it causes no perceptible retardation. 15% to 18%; the digestion is reduced by one-fourth to one-third. 20%; the digestion is strongly inhibited (Chittenden, Mendel, and Jackson, 1898).

Beers and wines have a slightly more unfavorable effect on account of the extractive matter contained in them.

(b) Effect upon Secretion of Digestive Juices.— Here also saliva and gastric juice need alone concern us.

Saliva: The presence of alcohol, strong or dilute, in the mouth increases the amount and the solids of the saliva, just as do many other substances (acetic acid, ether, etc.). This increased secretion does not take place if the alcohol is introduced directly into the stomach through a fistula.

Gastric Juice: The amount, the acidity, and the solids are very markedly increased, even when the alcohol does not come into direct contact with the gastric mucous membrane, but is introduced directly into the intestine. This juice is strongly proteolytic.

(c) Movements of Alimentary Canal.— These show a quickening.

(d) Effect upon Absorption.— The alcohol itself is very rapidly absorbed: 50 c. c. of a 20% alcohol disappear from the stomach of a dog in less than half an hour; and with the duodenum ligated, 200 c. c. of a 37% alcohol are completely absorbed from the stomach in three to three and a half hours. The absorption of other substances is also favored by it (Strychnin, Riemschneider, 1900).

Alcohol intended as antidote may therefore even increase the toxicity of poisons, if both are taken by the stomach, and this is not evacuated.

The effects upon the digestive organs are all merely expressions of its *local irritant action:* This produces, in mild stages, increased vascularity; and, partly as a result of this, partly through a direct action upon the cells, an increase of secretion, of movement, and of absorption.

To sum up, then, the experimental data bearing upon the effects of moderate doses:

The action of alcohol on digestion is a purely local one. Only gastric digestion need be considered, since the alcohol does not reach the intestine.

Moderate amounts tend to favor the process of digestion through an increased secretion of proteolytic juice, through increased gastric movement and increased absorption. With a percentage of alcohol above 15, these are counteracted by the lessened ferment action and by a harmful grade of irritation.

The actual result will depend upon which of these two — the beneficial irritant or the deleterious anti-ferment action

— predominates. Actual experiments on *intra vitam* digestion are not yet sufficiently numerous. But as far as they go, they show that in the dog the time required for the digestion of meat is about the same with and without alcohol; and metabolism experiments in man also prove that it does not diminish the utilization of food.

Small amounts of weak alcohol taken at meals cannot, therefore, have a bad effect upon digestion, and may even act favorably. The alcohol should not be taken in strength greater than perhaps 20%: even this would be too strong did it remain for any length of time; but it is absorbed so rapidly that this strength would very soon reach the favorable limit.

Large quantities of alcohol, however,— and especially when in concentrated form,— produce an irritation which surpasses the physiologic limit and interferes with the functions; and this is seen most markedly in chronic cases.

V. THE FATE OF ALCOHOL IN THE BODY.

Alcohol is absorbed very readily. Only a very small proportion is excreted, mainly by the urine and lungs. The balance, over 98%, undergoes complete combustion to CO_2 and H_2O. By the chemical energy thus liberated alcohol can perfectly replace carbohydrates and fats in the diet, and *is a typical non-nitrogenous food.* It is even superior to other foods in one particular, viz., in that it does not require digestion. By its poisonous side-actions, however, it may at first cause an increased nitrogen excretion in individuals not accustomed to its use; but this action disappears in a few days, and it then *saves nitrogen* like any other food.

The proportion of alcohol which is *excreted* unchanged depends somewhat on the dose, but it probably never exceeds 10%, and is generally less than 2%. The excretion takes place mainly by the kidneys and lungs. With large doses, a small amount may be found in the milk; but not with ordinary doses. None is excreted by the sweat or feces. The excretions do not contain an appreciable amount of intermediate decomposition products.

That *alcohol behaves in essential respects like other foods,* as far as nutrition is concerned, is shown by the following facts:

When added to an ordinary diet, the CO_2 excretion and the output of heat is not materially changed. The alcohol therefor saves the other constituents of the diet from decomposition, and the body shows a corresponding gain in weight. If it is added to a diet deficient in carbohydrates or fats, the metabolism is the same as if an isodynamic quantity of these foods were added.

Whilst there can be no doubt that alcohol is an excellent food, in the sense of being a source of energy, other factors must be taken into consideration. The increased nutrition may itself be detrimental to the body, either by preventing the complete combustion of metabolites (which may possibly be connected with the origin of gout), or by leading to an abnormal deposition of fat. A still more potent objection to considering alcohol as a generally useful food lies in its toxic action, especially its psychical effects. Alcohol can therefore be employed as a food only when a sufficient supply of energy cannot be obtained from an ordinary diet; as, for instance, in *digestive disturbances,* or when the demands on the organism are unusually large, as in *fever.*

The proverbial obesity of persons addicted to the over-use of weak alcoholic liquids (in which the nutrient effect is less obscured by the toxic actions), is a striking illustration that too good a nutrition is not necessarily beneficial. That alcohol lessens the oxidation of metabolites is shown by an *increased excretion of uric acid and ammonia* nitrogen at the expense of urea. This points to a modification of the functions of the liver (Paton and Eason, 1901).

Excessive doses of alcohol are always detrimental to nutrition, lessening both assimilation and disassimilation. The effects resemble those of the anesthetics.

VI. THERAPEUTICS OF ALCOHOL.

The most frequent internal use of alcohol is that of a "stimulant," using the term in its practical meaning. That the nature of this stimulation is not the same in all cases is sufficiently indicated by the fact that it is used in three very different conditions: in shock, in fever, and in debility. The manner in which the stimulation is brought about in these cases requires some further elucidation in order that the drug may be rationally employed.

1. In Shock, *especially traumatic; Hemorrhage; Sudden Weakening of the Heart; Snake-bite, etc.*— The value of alcohol in these conditions can scarcely be doubted. Its explanation is quite complex, since it acts in a number of ways:

(*a*) By producing a partial analgesia. Its psychic effect — the more cheerful and courageous condition of mind which it induces — is also of value.

(*b*) By the depression of the central nervous system which it produces in larger doses. Depressed centers are not so subject to shock, as is shown by the fact that extensive operations are much less apt to produce this condition under anesthesia.

(*c*) By a genuine reflex stimulation: With the usual way of taking the spirit, this occurs from the mucous membrane of the mouth and stomach. The same reflex stimulation may be obtained through the nose; spirit of ether is especially useful in this connection; and the smelling-salts also owe their action in part to alcohol. A more powerful reflex stimulation may be obtained by the hypodermic injection of alcohol or of ether, or of spirits of camphor (one or two syringes). This acts especially on the respiration (see Fig. 82 B). The effect on the blood pressure is uncertain (Fig. 82 A, page 430).

The stronger preparations of alcohol are the best for this purpose.

2. Use in Fever, *Chills, Inflammatory Conditions, etc.*—Alcohol acts here in the following manner:

(*a*) Through dilatation of the cutaneous vessels. This increases the loss of heat, removes blood from congested internal organs, and lessens the resistance to the work of the heart. This temporary relief of the heart is often all that is required to restore its powers, and the pulse will become more regular and stronger. The antipyretic action is not very lasting.

This action on the cutaneous vessels is possessed in still greater degree by Sp. Æther. Nitr., which in so far may take the place of alcohol.

(*b*) Through its narcotic action, counteracting the nervous phenomena of fever and inducing quiet and rest. This in turn diminishes the demands made upon the strength of the patient.

(*c*) Its action as a food: The metabolism in fever is very greatly increased, and the assimilative powers at the same time diminished. Whilst this increased tax falls very largely upon the nitrogenous part of the body, the drain upon the carbohydrates and fats is also very serious. And these last can be met very largely by alcohol, which possesses the advantage over ordinary foods of very ready absorption.

(*d*) The diuresis may be useful in removing toxins, etc.

The employment of alcohol in fever must still be looked upon as largely empirical; for it is impossible to tell *a priori* to what point its depressing action on the central nervous system will be useful and where it will begin to be detrimental. The individual observations in each case can alone guide its employment: As long as it improves the prominent symptoms, the dose may be increased. As soon as it ceases to do so, it should be diminished or stopped. It is frequently astonishing to see the quantity which is borne without harm in fever and without producing "intoxication." This must be attributed largely to its more rapid oxidation. The amount given must, of course, also be governed by the previous habits of the patient.

With regard to the use of alcohol against *chills and exposure,* it must be reiterated that the time for taking it is after, not during, the exposure. If the latter is done, the temporary relief and feeling of warmth is obtained at the expense of an increased loss of heat, and consequently diminished power of resistance. But if taken after the exposure, the dilatation of the cutaneous vessels favors the absorption of external heat, and also prevents the tendency to congestion of internal organs.

In all these conditions the alcohol is taken in the form of the spirits, diluted with at least equal amounts of water.

3. In Convalescence and General Debility.— The value of alcohol in these conditions is established by long experience. Its action must be quite complicated. There is, in fact, no organic lesion, and in all such cases a great deal may be expected from improving the symptoms. This, like nursing and hygiene, increases the comfort and well-being of the patient, and starts him on the way to improvement. Alcohol meets these indications in an excellent manner: The feeling of well-being caused by it, the enjoyment in the act of taking it, the rest and sleep induced by its narcotic action. its food-value and its beneficial effects upon digestion, all concur in its action. To this may be added its slight but certain effects upon the vascular system,— the altered distribution of blood, the diminished resistance to the heart, — which may be of benefit in some cases.

For these purposes, alcohol is usually taken in the form of light wines.

4. The narcotic and hypnotic effects of alcohol are also utilized, the former in melancholia, neuralgia, and some other obscure nervous diseases; the latter in insomnia. Whilst the effects are undoubtedly beneficial, there exists a very great danger of inducing chronic alcoholism, especially in the first class of cases. It must certainly be used with very great caution. The stronger spirits are best adapted for obtaining the narcotic effect; beer, for the hypnotic.

5. Indigestion.— From what was said on page 413 it will be easily understood that it does not act equally well in all cases. Whilst the clinical interpretation of the various forms of indigestion is not as yet so perfect as to enable us to tell the pathology of those cases in which alcohol is useful or not, it might be expected to be of benefit where there is a faulty circulation, whilst it would be harmful where the amount of ferment secreted is small and not capable of increase, as also in hyperacidity. Certain wines become injurious on account of their acidity. The tannin, which is present particularly in red wines, may be detrimental to digestion, but valuable in diarrhea. Brandy is also used against diarrhea. This probably rests upon the beneficial effects of an increased circulation.

Champagne is also used as an antemetic. Its action in this case depends upon the CO_2 rather than on the alcohol.

6. The **diuretic action** of alcoholic beverages (beer and gin) is sometimes utilized. It is claimed, however, (A. Raphael, 1894), that the diuretic action of a liter of beer or wine is the same as that of the same quantity of water, and less than that of milk. Larger quantities of alcohol, however, have a distinct diuretic effect.

As **contraindications** to the internal use of alcohol may be mentioned:

The danger of forming a habit.
Gastric irritation.
Urethral disease or nephritis.

7. The **local actions** of alcohol are also frequently used. The cooling produced by its evaporation is very grateful in *fever,* and it is frequently used for sponging the skin. The local use of alcohol is of further benefit in this condition by preventing the development of bedsores through its mild irritant action. The same property determines its use on ulcers. Used in a more concentrated form and kept from evaporating, it acts as an excellent rubefacient, and, in the form of tinctures, it forms an important ingredient of most liniments.

It is scarcely necessary to refer to the great pharmaceutic importance of alcohol, depending upon its solvent powers.

It must be remembered that it forms an ingredient of very many pharmaceutic products — tinctures, fluidextracts, and spirits.

VII. HABITUAL USE OF ALCOHOL.

It may be considered as proved — some authorities to the contrary notwithstanding — that a certain amount of alcohol (variable in individual cases) may be taken daily without any demonstrable permanently injurious effect. But it stands equally certain that it is as dispensable to the organism as nicotin or caffein, and that it must be looked upon purely as a luxury. The injury done by such use of alcohol lies alone in the fact that it is so apt to lead to the use of immoderate amounts.

With such excessive use a train of phenomena results, which may be grouped together under the name of chronic alcoholism, and which depend in part upon the irritant action of the alcohol, in part upon specific injury to the neurons.

The first effects are *local,* and depend largely upon the concentration of the spirits. They consist of a *catarrh of the whole alimentary canal,* progressing from the pharynx downward. They are characterized by the usual symptoms of catarrhal gastro-enteritis: loss of appetite, gastric distress, irregularity of stools, longing for spices, etc. The chronic catarrh leads to malnutrition and emaciation when strong spirits are used. It also appears to constitute a predisposing factor to carcinoma of these organs. In the case of excessive beer-drinking the habitual overdistention of the stomach leads to chronic dilatation.

The continued presence of alcohol in the body sets up a series of *irritant and degenerative phenomena in various other organs* with which it comes in contact. These changes consist in fatty infiltrations, cellular degenerations, and hypertrophy of connective tissue. The necrotic changes in the tissue cells must be attributed to the continued irritation from the constant presence of the alcohol; and to this must be added the interference with circulation due to the changes which alcohol causes in the blood-vessels. These two — the direct irritant action of alcohol on the cells, and the impaired circulation — are inseparably connected in the production of the degenerations. Of these, the fatty are the most common, since alcohol, by its combustion, prevents the normal consumption of fat. Connective-tissue formation results as the ordinary consequence of necrosis of the parenchyma.

These changes are proportional to the *concentration* of the alcohol. And since this is naturally greatest in the liver, kidneys, and blood-vessels, these organs show the action first and most prominently. And in the liver, again, the *periphery of the lobules* is mainly affected, on account of the anatomic relation to the portal vein.[1]

Next in point of time comes the action on the *blood-vessels*. This is of especial import, since it contributes materially to the degenerations in other organs. The principal changes are in the intima: there are fatty degenerations, loss of elasticity, and atheroma.[2] These may lead to ruptures (apoplexy, etc.).

The degenerative changes in the *kidneys* lead to nephritis, with cirrhosis, albuminuria, diminished secretion of urine, secondary weakening of the heart, etc. The *heart* itself, however, in common with skeletal muscle, shows primary fatty degeneration. This, together with the atheroma, etc., leads to hypertrophy and dilatation of the viscus, and later to dropsies, etc. The fatty changes in *voluntary muscle* lead to muscular debility, especially in beer-drinkers, in whom there is more material for fat formation. *Gout* is a common sequence of moderate alcoholism.

The *respiratory organs* show a chronic catarrhal inflammation of the passages, and a disposition to fatal pneumonia. Changes in the skin — vascular ecchymoses, acne rosacea, disposition to furuncles and carbuncles — may be counted amongst the earlier actions.

These various anatomic lesions of important organs result in a pronounced lowering of the "powers of resistance," and a high mortality with infectious diseases, operations, etc. Part of this may be due to a lowered alkalinity of the tissues through the partial oxidation of alcohol into fatty acids. It appears also that the amount of *antitoxic complement* is lessened.

The effects of chronic alcoholism upon the **central nervous system** differ from the above in that they are partly functional. Too great stress cannot be laid upon the importance of habit and repeated impressions on the psychic activities. The constant repetition of the features of alcoholic excess could not but produce in this manner a permanent moral degeneration. But associated with this functional feature are marked organic changes, due to the same causes as similar changes in other organs; and, lastly, it must be remembered that alcohol has a specific action on the nerve-cells.

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[1] It is claimed that the degeneration of the liver can be avoided in animals by the administration of cane-sugar.

[2] As a result of an extensive study of autopsy material, Cabot (1904) disagrees with the common opinion that alcoholism is a cause of arteriosclerosis.

Amongst the organic lesions which have been observed are: Chronic meningitis with thickening; serous effusions into ventricles; softening; tendency to hemorrhages and apoplexy. Histologically, shrinkage and alterations in the staining properties of the cells (Fig. 80) and changes in the dendritic processes have been averred.

Clinically, the first effects are shown by a diminished activity of the individual. This occurs even with very moderate doses. Later there is a diminished acumen of the special senses and of the reasoning powers, leading, the former to disturbances of vision, the latter to degeneracy and dementia, often suicidal. It is a noteworthy fact that by far the greater proportion of inmates of insane asylums and prisons were addicted to the excessive use of alcohol. In how far alcohol is responsible for the population of these institutions — whether the abuse of alcohol is really the cause of these conditions or only another effect of the underlying disease — cannot be decided at present.[1]

On the part of the motor system there are tremors, and later convulsions and paralyses, the latter partly the result of peripheral neurites.

The influence of alcoholism in the parent on the *offspring* is a question not yet definitely answered. It is certain that the nutrition and resisting power of the offspring are greatly impaired by it. The mortality amongst the children of alcoholics is very high. It is also certain that psychic degeneracy — epilepsy, idiocy, predisposition to crime and to the abuse of alcohol — are extremely common in them. But it cannot be decided whether it is the degeneration induced in the parent by alcohol, or the degeneration underlying the abuse of alcohol, that is inherited. The latter is the more likely.

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[1] 10 to 30% of the cases of insanity are attributed to the abuse of alcohol.

It is claimed by Von Bunge (1904) that chronic alcoholism on the part of the father renders the daughter incapable of efficient lactation, and that this incapacity, as well as a tendency to tuberculosis and to caries of the teeth is transmitted to subsequent generations. But if this danger is really as great as it is painted, it is difficult to account for the comparative vigor of populations amongst whom chronic alcoholism has been fairly common for many centuries.

When alcohol is taken by the mother, it passes across the placenta in such amount as to exist in the same concentration in the blood of the fetus as in that of the mother.

Alcohol is not the only member of the hydrocarbon series which has been abused as an intoxicant. Ether, chloroform, chloral, and even turpentine and gasoline have their devotees. Their effects, in so far as they have been studied, correspond closely to those of alcohol.

VIII. TREATMENT.

The *treatment of acute alcoholism* consists in evacuation of the stomach and nervous stimulants, caffein or strychnin. The subsequent headache and nervousness are met by bromids, caffein and acetanilid. Sodium bicarbonate lessens the gastritis.

Chronic alcoholism can only be treated by withdrawal of the drug. Medication is of use only in meeting the symptoms. Irritants — especially capsicum — are useful in replacing the local action of alcohol; the depression should be met by caffein, the insomnia by bromids. Suggestion may be very useful.

IX. DELIRIUM TREMENS.

A peculiar disease, specifically characteristic of chronic alcoholism, remains to be mentioned, namely *delirium tremens.* This occurs in chronic alcoholics whenever their forces are unusually weakened — by an extraordinary excess or by the suppression of their usual allowance of alcohol; by absence of food; by exposure or overexertion; by an operation, etc. The symptoms consist in violent tremor, persistent insomnia, and hallucinations of a terrifying character. It usually runs its course in a few days. The main indications of treatment are to support the strength of the patient and to combat the excitement and insomnia by hypnotics, as bromids, chloral, or opium. It is not deemed advisable to withdraw the alcohol entirely during this condition.

X. MATERIA MEDICA.

Preparation of Alcoholic Liquids.—Alcohol is a product of the alcoholic or vinous fermentation of liquids containing certain sugars (especially dextrose). This fermentation is produced by the growth of the yeast plant—*Torula cerevisia.* These sugars exist preformed in the juice of the grape and in other fruits. Alcoholic beverages are also prepared from starchy grains, etc., the starch being first converted into sugar by malting, etc. The process is described in text-books of chemistry.

It was formerly supposed that the bouquet of the different sorts of wines, etc., depended upon differences in the constituents of the grape-juice; but it is now known that they are caused rather by differences in the yeasts infesting these grapes. The inoculation of a barley infusion with a wine yeast gives to the fermented liquid the peculiar flavor of that particular wine (the so-called "Malton Wines").

As ordinarily prepared, however, the character of the fermented liquids depends upon their origin. When made from barley, they are beer, etc.; from apples, cider; from grapes, wine; from milk, kumiss, etc.

Most of these, as well as the distilled spirits, undergo further chemic changes on keeping, resulting in the destruction of undesirable constituents ("impurities"—fusel oil, etc.) and in the development of ethers, etc., imparting a finer flavor to the liquid.

The alcoholic fermentation only progresses to a certain point; beyond this, it is either arrested entirely, as soon as the proportion of alcohol exceeds a certain amount; or it passes into acetic fermentation, with the conversion of the alcohol into acetic acid.

When these weak liquids are subjected to distillation ("rectification"), the stronger "alcoholic liquors" result. These receive different names according to their origin:

Whisky, when distilled from fermented grain (this rectified over juniper berries is *Holland Gin;* over turpentine, *Common Gin*); from wine, *Brandy* (*Cognac*); from molasses, *Rum;* from rice, *Arrack,* etc.

Further redistillations result in the official alcohol; and by redistilling from some hygroscopic substance, usually quick-lime, the so-called "Absolute Alcohol" is obtained.

The strength of alcoholic liquids is deduced from the specific gravity after distillation.

(A) Pure Alcohols:	Specific Gravity. (15.60° C.) (60° F.)	Per Ct. Weight.	Per Ct. Volume.
Alcohol (U.S.P.) [Spiritus Rectificatus, B.P]	0.816 (U.S.P.)	92.3	94.9
	0.834 (B.P.)	91.0	94.0
Alcohol Absolutum (U.S.P., B.P.). Not more than 1% by weight of water. Boiling-point, 78.4	0.797	99.0+	
Alcohol Dilutum (U. S. P.). Made by mixing equal measures of alcohol and water	0.936	41.5	48.9
Alcohol (70%) (B. P.). Made by mixing 100 vol. of alcohol (90%) with 31 vol. of water	0.8900		70.0

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(A) Pure Alcohols:	SPECIFIC GRAVITY. (15.60° C.) (60° F.)	VOLUME. PER CT.
Alcohol (60%) (B. P.). Made by mixing 100 vol. of alcohol (90%) with 53.65 vol. of water	0.9135	60.0
Alcohol (45%) (B. P.). Made by mixing 100 vol. of alcohol (90%) with 105.34 vol. of water	0.9436	45.0
Alcohol (20%) (B. P.). Made by mixing 100 vol. of alcohol (90%) with 355.8 vol. of water	0.9760	20.0

Since a condensation occurs on mixing alcohol and water, the percentage of the resulting produce cannot be deduced by the formula $\% \div (V + V)$.

The quantities needed to make the most common dilutions are the following:

TO MAKE 100 C.C. OF:	USE *Official* (U. S. P.) ALCOHOL:	WATER:	SPECIFIC GRAVITY. (15.6° C.) (60° F.)
80% (volume)......	85.5 c.c.	16.0 c.c.	0.8642
70%	73.5 c.c.	29.0 c.c.	0.8903
60%	63.5 c.c.	39.0 c.c.	0.9135
50%	53.5 c.c.	49.5 c.c.	0.9344
40%	43.0 c.c.	60.0 c.c.	0.9520
20%	21.3 c.c.	80.1 c.c.	0.9759

(B) Stronger Spirits:

Spiritus Frumenti (U. S. P.).—*Whisky.*—By distillation of the mash of any fermented grain (should be at least two years old). Sp. G. 0.924 to 0.945. Alcoholic strength, 37 to 47.5% weight, 44 to 55% vol.

Spiritus Vini Gallici (U. S. P., B. P.).—*Brandy* (*Cognac*).—By distillation of fermented grape-juice. Sp. G.=0.925 to 0.941%; alcoholic strength, 39 to 47% weight, 46 to 55% vol.

Mistura Spiritus Vini Gallici (B. P.).—Four ounces each of brandy and cinnamon water, two yolks of eggs, and ½ ounce of sugar.

The percentage of other stronger liquors are:

	VOLUME.	WEIGHT.
Rum	50	42
Gin	48	40
German "Schnapps"	45	38
Russian "Dobry Wutky"............	62	54

(C) Weaker Alcoholic Liquids:

The only ones official are:

Vinum Album (U. S. P.).—*White Wine.*—A dry white wine, such as Catawba. 8.5 to 15% by volume.

Vinum Rubrum (U. S. P.).—*Red Wine.*—Dry red wine such as native Claret or Burgundy. 8.5 to 15% by volume.

Vinum Xericum (B. P.).—*Sherry.*—A pale wine containing not less than 16% by volume of alcohol.

Wines are made by fermenting the expressed juice (must) of the grape. If this contains the skins of dark grapes, the wine will be red: if made from light grapes, or from the juice of dark grapes without skins, it is "white"; *i. e.*, an amber color.

A wine which contains much alcohol (15% to 20%) is "generous"; one poor in alcohol, "light"; one containing much sugar, "sweet";

poor in sugar, "dry." If it contains CO_2, it is "sparkling"; if tannin, "rough" or "astringent"; if acid tartrates, "acidulous." The last two ingredients will interfere with digestion if the wine is habitually used.

The most important wines are:	Alcohol. Per Cent. Weight.	Alcohol. Per Cent. Volume.
Sherry (Vinum Xericum): Dark amber, dry, little acidity (*Madeira*, Marsala, Tokay, Malaga, are similar, but more sweet)	15 to 19	18 to 23
Port (Vinum Portense): Deep purple, rather sweet and rough		
Claret (Bordeaux): Red, dry, with some degree of acidity and astringency	8 to 14	10 to 17
Champagne: Pale amber, sweet, sparkling.	8 to 10	10 to 13
Hock and Moselle: Pale amber, dry, slightly acid	12	15
Catawba: Amber, dry, rather acid (or sweet)	10 to 12	13 to 15

Unfermented Grape Juice (*i. e.*, must, preserved by heating or an antiseptic) can scarcely be considered a medicinal agent.

Other Fermented Liquors:

From Apple: *Cider*,	5 to 10% (by weight).
From Pear: *Perry*,	
From other fruits,	

Malt Liquors.—These contain alcohol, CO_2, sugar, and usually hops. The color varies from pale amber to dark brown, the difference being due mainly to charring of the malt. Lager beer is made by slow fermentation at a low temperature; porter, ale, and stout by rapid fermentation at a higher heat.

Their alcoholic strength is as follows:

Ale, Porter, Stout, and Export Beer	3 to 6%	by weight.
Lager Beer	2 to 3%	

By fermenting milk, a pleasant alcoholic liquid, "*Kumiss*," can be obtained, which contains to 3% of alcohol.

Mixed Spirits.

It must be remembered that all the alcoholic preparations — Fluidextracts, Tinctures, Spirits, and Elixirs — whose dose contains more than about 5 c. c. of absolute alcohol show the action of the latter.

Some of the pharmaceutic preparations which are employed largely on account of their content of alcohol are the following:

	Approximate Alcohol Content.
Elixir Aromaticum	25%
Spiritus Juniperi Compositus (a substitute for Holland Gin)	65%
Vinum Ferri Amarum	15%
**Cordiale Rubi Fructus* (*Blackberry Cordial*), N. F.	33%
**Elixir Adjuvans*, **Elixir Anisi, and other Elixirs*, N. F.	25%
**Vinum Aurantii; V. Carnis; V. Cocæ*, etc.	16%

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* Not official.

(C) THE CHLOROFORM AND ETHER GROUP.

I. HISTORY.

Attempts to induce anesthesia during operations date back to very ancient times. The Egyptians gave narcotic potions for the purpose. The Assyrians are said to have half strangled the children before circumcision, producing anesthesia by the aid of the CO_2. The Chinese used hashish. All kinds of narcotics were given during the middle ages.[1] But modern anesthesia dates from the middle of the nineteenth century. Its discovery is claimed by quite a number, but the real credit of introducing anesthetics into practice belongs, for ether, to Jackson (1841) and Morton (1846); and for chloroform, to Simpson, in 1847. Soon afterward laughing gas was introduced, although this had been suggested by Davy fifty years before.

II. DETAILS OF ACTION.

The *action* of this subgroup corresponds very closely to the general action which has been discussed on pages 401 to 406.

The *difference from alcohol* consists in the greater rapidity with which the successive stages may be induced. Of the different members of the series which might be used for the production of anesthesia, chloroform and ether are the most important, and the following description applies particularly to them.

The action of the anesthetics has been divided into *different stages*. Since these are but degrees of the same action, it is quite optional where the line is drawn, and the same stages will be retained here that were given in the discussion of the general action: viz., Stimulant, Narcotic, Anesthetic, and Paralytic.

1. Stimulant Stage.— This sets in with a comfortable *feeling of warmth,* spreading over the whole body, soon associated, however, with a *sensation of asphyxia.* The *local effects* make themselves felt by *pricking and smarting of nose, throat, and conjunctiva.* Consequently there is a *hypersecretion of mucus, tears, and saliva,* and *possibly vomiting;* but the latter does not usually occur until much later, when the patient has been some time under deep anesthesia and this is passing off. The *face* at this stage is *flushed,* the *pupils somewhat enlarged,* the *pulse accelerated,* the *respiration somewhat quickened* and irregular — all effects of the excitement.

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[1] Especially opium and drugs containing hyoscin (such as Mandragora officinalis). This has been recently revived in the Schneiderlin method (see Index).

2. The second or **narcotic stage** is ushered in by formication. The *special senses are disturbed;* there are *hallucinations* (noises, etc.). Sensation of stiffness and want of control in the muscles. The patient loses his *self-control,* and gives way to manifestations which vary with his character — loud talking, laughing, singing, swearing, etc. Then there is *struggling,* and sometimes, especially in hysteric patients, *convulsions.* These motor phenomena are much more violent than in the case of alcohol, probably on account of the greater local irritation and also because of a certain amount of asphyxia. They differ greatly in violence in different individuals. The *skin is moist and warm,* the *face reddened,* the *pupils contracted,* the *apex-beat more pronounced.* The *sensibility to pain* is *blunted, but not abolished.*

3. The third or **anesthetic stage** — the stage which it is aimed to produce and maintain — is characterized by complete paralysis of the brain and of the motor reflex centers of the cord, and lowering of the medullary centers. *Consciousness, sensation, and most reflexes are lost* — the *corneal reflex* being among the last. Consequently the muscles are lax. The smooth muscles are not usually affected, but there is sometimes a relaxation of the sphincters. The *pulse is slow, full, and soft,* due to *lowered blood pressure.* The *respiration is slow and shallow,* but *regular.* The *temperature falls* in consequence of the lessened muscular activity and increased heat loss. The *face* is pale with chloroform, often cyanotic with ether. These symptoms of medullary paralysis do not reach a dangerous degree if the administration is carefully done. But with *prolonged anesthesia* the pulse tends to become progressively weaker, the respiration more shallow, and the temperature lower — it may fall as much as 5° C. This is due to paralysis of the function of temperature-regulation.

There is some evidence that the sensory cells are paralyzed before the motor, since at certain stages of the action reflex paths which have their sensory and motor cells in different parts of the cord may be excited if the motor, but not the sensory, cells are exposed to the action of the anesthetic. But later the motor cells also lose their irritability. The excitability of the *motor area* of the brain is lowered.

4. The fourth or **paralytic stage** is characterized by progressive paralysis of the medulla. This stage must be carefully guarded against.

The *respiration* becomes irregular, stertorous, labored, and then ceases. The *skin* is cold and pale, and covered with the cold clammy sweat of the "agony." The *pupils* are widely dilated. The *pulse* becomes slow and weak, and ceases normally after the respiration.

5. During the stage of *recovery*, after the anesthetic has been removed, the patient again passes through a stage of excitement, much less violent than in the second stage. Then there is usually a *sleep* lasting for several hours. *Vomiting* is very common during recovery, when the irritation of the alimentary canal is no longer masked by the depression of the centers. Thirst and gastritis persist for some time.

6. Phenomena Indicating Onset of Paralytic Stage.— Since *Accidents in Anesthesia* are generally due to the onset of the paralytic stage,— *i. e.*, to paralysis of the medullary centers,— it is important to study more in detail the symptoms which usher in this condition. It will be profitable to follow these from the beginning of the anesthesia. They refer to the respiration, circulation, and pupil.

Respiration.— This is fairly normal in the *first stage*, except in so far as it is interfered with by the choking produced by the local action. This latter, through stimulation of the trigeminal endings, may also produce a short stoppage, but this is never very long (it does not appear after section of the vagi in animals). During the *second stage* the respiration is affected by the struggling, being alternately stopped and quickened. In the *anesthetic stage* it is very slow, but regular. With the approach of the *fourth stage* it is first quickened as the result of asphyxia. *The danger-sign is the irregularity.* The death by anesthetics is in most cases due to asphyxia. But this, except with the most ignorant administration, is not due primarily to a want of air, but to paralysis of the respiratory center.

Circulation.— The effect of anesthetics on the circulation is complicated, and varies for the different anesthetics, since it depends upon several factors, which vary quantitatively for the different drugs, and according to circumstances.

During the *first and second stages* there is generally a quickening of the pulse and a rise of blood pressure (Fig.

81 *A*), mainly from the increased movement, but partly from a slight depression of the vagus center. The face becomes flushed. A considerable rise of pressure may occur from incipient asphyxia (Fig. 81 *B*). In rare cases, there may be a temporary slowing or even stoppage of the heart, from reflex stimulation of the vagus center through the trigeminal endings (Fig. 81 *A*). This may be prevented by atropin, or by cocainizing the nasal mucosa.

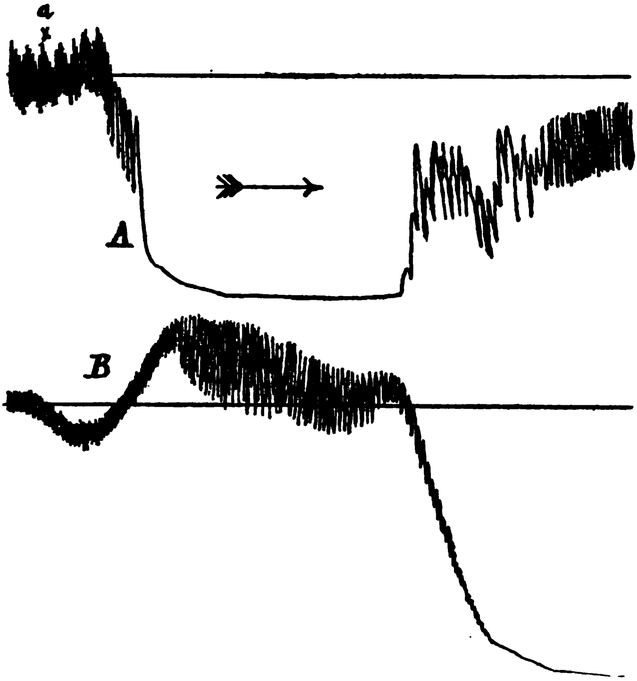

FIG. 81.—Accidents of anesthesia: A. Reflex stoppage of heart; blood pressure, dog. Ethyl chlorid is inhaled at a. The heart and respiration stop promptly (trigeminus-vagus reflex). They resume spontaneously after two minutes. B. Direct paralysis of the heart, preceded by asphyxial rise. Ethyl chlorid inhalation, blood pressure, dog.

In the *third stage*, the pulse is rather soft and slow, but regular. The blood pressure is scarcely altered, or may even show a slight rise, when ether is employed (Fig. 82 *C*). Ether therefore has but little effect on the vasomotors. With chloroform, A. C. E. mixture, and ethyl chlorid, there is a considerable fall, due to depression of the vasomotor

center, the heart being but little altered (Fig. 82 *D*
If asphyxia supervenes, the pressure may rise co
with ether and ethyl chlorid, but not with ch
since the cardiac and *vasomotor depression* are

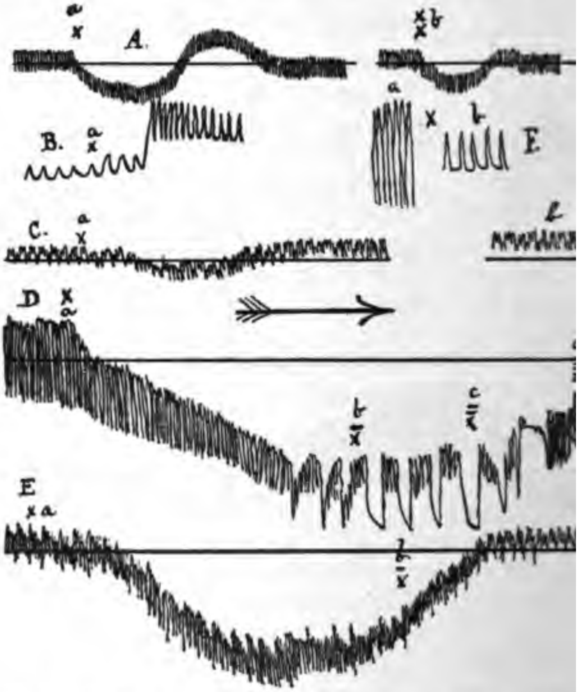

FIG. 82.—Alcohol and Anesthetics. A, Blood pressure, dog.
whiskey intravenously at (a) and (b). Slight temporary fall; followe
small and temporary rise in (a), not in (b). B, Respiration of ane
bit (pneumograph). At (a), 2 c. c. of *whiskey hypodermically*. St
increase of rate and depth of respiration. C, Ether on blood pr
The animal is very lightly anesthetized at the beginning of the
ether is pushed at (a). There is practically no effect on the b
even after ten minutes (b). D, *Chloroform on blood-pressure* (do
halation is begun at (a) and pushed. The pressure falls, without
change in the heart (central vasomotor depression). The anesth
drawn at (b). The respiration is very shallow. Artificial respirati
at (c) and stopped at (d). The original pressure is gradually
Ethyl chlorid on blood pressure (dog). The inhalation is continued
The effects are very similar to those of chloroform. F, *Chloral on*
cardiogram, dog; (a) normal, (b) after chloral. The beats are
weakened.

nounced with the latter drug. It is possible that
motor endings and the arterial muscle are also dep
chloroform, especially in the intestine and kidney
and Martin, 1905); some other vessels, however,

stricted by chloroform (Schaefer and Scharlieb, 1904). On account of the extensive vasodilatation, the skin becomes pale in chloroform anesthesia, but not with ether. The excitability of the vagus endings is depressed. The heart muscle is but little affected at this stage, even by chloroform.

In the *fourth stage*, the vasomotor depression becomes pronounced, even with ether. This is due partly to a direct action on the vasomotor mechanism, but is also aided by the asphyxia. It is the usual cause of death. The pulse becomes very soft and irregular (Fig. 82 *D*). At this time the cardiac muscle is but little affected, except indirectly, *i. e.*, through the asphyxia and low blood pressure. Removal of the anesthetic, artificial respiration, and brisk massage of the heart (*i. e.*, rapid and strong rhythmic compression of the cardiac region) will usually cause prompt recovery (Fig. 82 *D*). The patient must, however, be carefully watched, even when recovery seems complete.

If chloroform is pushed very rapidly, it acts directly on the cardiac muscle. Recovery is then much more difficult, or even impossible.

The direct action on the heart-muscle has been studied by perfusion of the excised heart (Langendorff method).[1] The effect is *very much greater with chloroform* than with ether. It occurs very promptly (within two minutes) and consists in a lessened force of the contractions, the rate being but little altered (Fig. 82 *F*). The auricles are less affected than the ventricles. The effect is proportional to the concentration of the chloroform, and independent of the absolute quantity and of the time of perfusion. The heart recovers at once when the chloroform is removed, unless the concentration was excessive (0.15%), in which case fibrillary contractions appear and recovery is impossible. Ether has much less action, and alcohol is practically harmless even when 2% is present.

Pupils.— These are dilated during the *first and second stages*, as the ordinary result of excitement. During the *anesthesia* they are strongly constricted, due to depression of the dilator center, and to the cutting off of afferent impulses, as in sleep. In the *fourth stage*, asphyxial stimulation of the center causes dilatation. Dilatation also occurs in *recovery*. The danger-sign, therefore, is dilatation of the pupils, unless this accompanies evidence that the patient is coming out of the influence.

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[1] See especially Sherrington & Sowton, Suppl. British Medical Journal, 1903, p. 147.

III. CAUSES OF DEATH UNDER ANESTHESIA.

In the later stages of the anesthesia this usually results from *medullary paralysis,* aided by direct paralysis of the heart muscle, and, as has been pointed out, the respiration normally gives out before the other centers or the heart. But it must not be forgotten that the latter are also weakened, and would eventually lead to death even were the respiration kept up. The respiration is simply the weakest link in an interlocking chain, and when another link is abnormally weak, it may give out first. In cases in which the heart is not normal, this may and does give out before the respiration.

But in another class of fatal cases especially with chloroform, the course of events may be entirely different:

Here the heart stops suddenly, often when only a few whiffs of the anesthetic have been taken. This is especially apt to occur when the patient has been struggling or holding the breath. The chloroform is forced tighter upon him, and when a respiration is taken, the vapor is inhaled in almost undiluted form. Now, the concentration, and not the total quantity, of the anesthetic constitutes the primary element of danger. This concentrated anesthetic vapor may produce sudden stoppage of the heart in two ways:

1. By reflex stimulation of the vagus through the trigeminus endings. This, though very alarming, is not usually dangerous with normal individuals, for stimulation of the vagus cannot stop the heart sufficiently long to constitute an element of danger. In fact, this is a safeguard, in not allowing the concentrated anesthetic to be carried to the heart. But with a weak heart and depressed circulation this temporary stoppage may turn the scale. This vagus stoppage does not occur when the anesthesia is well advanced, since all reflexes are diminished at this time. Besides, anesthesia causes a lowering of the irritability of the vagus endings in the heart.

2. The vapor is carried by the blood in very concentrated form to the heart, which it paralyzes through its direct action on the muscle. This is almost invariably fatal. Concentrated vapor, then, generally paralyzes the heart, whilst diluted vapor paralyzes the respiration.

Another cause of unpleasant symptoms of an irritant character lies in the *impurities* resulting not only from imperfect manufacture, but from the decomposition of the pure product. This decomposition is especially frequent with chloroform, resulting in the formation of Phosgen gas and of free Cl and HCl, all very irritant.

$$4CHCl_3 + 3O_2 = \underset{\text{Phosgen.}}{4COCl_2} + 2H_2O + 2Cl.$$

$$COCl_2 + H_2O = CO_2 + 2HCl.$$

As this is greatly favored by exposure to light, chloroform should be kept in small dark-colored bottles. The addition of 1% of alcohol greatly retards this decomposition, but when chloroform is used with artificial light, the combustion of its vapor necessarily results in these products. It would, therefore, be advisable to use incandescent electric light, which, in the case of ether, would also obviate the danger of ignition.

Of course, many deaths during anesthesia are due to the inexperience of the anesthetizer, some possibly to impurities,[1] a few are undoubtedly unavoidable. But it is incorrect to attribute every death upon the operating table to the effects of the anesthetic; for patients died upon the table when anesthetics were yet unknown.

One such case was of considerable importance in the history of anesthesia. When Simpson was about to try chloroform on a patient for the first time, the orderly who was carrying the bottle fell and spilled the chloroform. No other being obtainable Simpson proceeded to the operation, which was for hernia, without anesthesia. The patient died with the first cut. Had the chloroform been given in this case and the same accident had happened, its introduction into practice would have suffered a long delay. Other similar cases are not uncommon: A patient was to be operated and demanded chloroform. His condition, however, was so low that the surgeon feared to grant his wish, and to calm him held a cloth *without* chloroform before his face. Scarcely had the patient made four inhalations — of air — when he was dead. In preanesthetic days, the French surgeon Desault drew his fingernail over the perineum of a patient to mark the line of incision, when the patient suddenly gave a cry and was dead. And many similar cases of sudden death from the violent mental impression might be mentioned, besides deaths undoubtedly due to traumatic shock. Even at the present day patients often exhibit "psychic shock" when operated under local anesthesia, so that it is a general practice to precede this by morphin (Strassmann, 1898).

It is true that the public nowadays has largely lost the great fear for operations and that anesthetics lessen the danger of traumatic shock. But neither is excluded, and there is no doubt that many deaths attributed to anesthetics have their cause elsewhere.

The *autopsy* in acute chloroform or ether deaths shows nothing beyond the ordinary phenomenon of death by asphyxia — heart distended, veins congested, etc.

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[1] It may be doubted whether any fatal effect can be ascribed to the impurities.

Idiosyncrasy.— There can be no doubt that the dangers of anesthesia vary in different individuals. These differences are also seen in animals. The zone of safety is especially small in alcoholic and hysterical patients. The difficulty is mainly one of administration, struggling and irregular respiration making it impossible to dose the anesthetic correctly. This may be largely obviated by morphin. Sometimes a patient will take one or the other anesthetic more readily. It seems probable that idiosyncrasy may exist, even when the administration is uniform; but of this there is no good proof. Mansfeld (1905) claims that starved animals are much more susceptible to chloral, paraldehyd, and morphin, but not to alcohol, amylen hydrate, or urethane.

In connection with anesthetics there is a question of some medico-legal importance — namely, whether anesthesia can be produced during sleep. Such cases are reported, but it must be extremely difficult, and consequently rare.

After-Effects, Side-Actions and Effects on Metabolism.— A certain amount of *gastric irritation* is a constant phenomenon, but rarely assumes serious features. So is an irritation of the *respiratory* structures, which is further complicated by a lowered resistance of the lungs, which, with the inspiration of saliva and buccal bacteria, may give rise to pneumonia. Previous disinfection of the mouth has therefore been recommended. The occurrence of other infections is likewise favored by the temporary lowering of the powers of resistance. Evidences of an *acute nephritis* — albuminuria and glycosuria, sometimes casts — are not uncommon, but may in some cases be referred to asphyxia.

These after-effects are more pronounced in the case of ether than of chloroform; for although, quantity for quantity, chloroform is by far the more irritant of the two, the absolute amount of ether taken more than balances this difference.

The question whether ether or chloroform is more irritant to the kidney cannot be considered as decided.

Recovery occurs most promptly and with the least after-effect with nitrous oxid and ethyl chlorid; then comes ether, and lastly chloroform.

Chloroform and chloral occasion very pronounced changes in **metabolism,** shown especially in an increased excretion of non-urea nitrogen and of organic sulphur (especially in carnivorous animals).[1] The glycogen of the liver is diminished, the sugar of the blood is increased, and glycosuria is frequently seen. These effects are due specifically to the chloroform, and not to the anesthesia. The effects of ether resemble those of alcohol. Chloroform, ethyl chlorid, and nitrous oxid lower the CO_2 of the blood and increase its oxygen. Croton-chloral and chloralose have the opposite effect. The anesthetics of this series cause a laking of the *blood* outside of the body, and there seems to be a slight effect of this kind in the body: examination of the blood shows a polycythemia, due to diminution of the plasma. The hemoglobin is, however, reduced. Some corpuscles are destroyed entirely, others lose only part of their hemoglobin. Since a diminution of hemoglobin to 50% is dangerous, it is never safe to use anesthetics on patients showing only 60% of hemoglobin (Da Costa and Kalteyer, 1901).

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[1] The effects of chloroform are described by Rostoki, 1901; those of ether by Pringle & Maunsell, 1905; ether glycosuria by Röhricht, 1905.

It is conceivable that this hemolysis explains partly the *anemia and icturus* which are sometimes seen; but these may also be caused by hepatic changes. The liver-cells show marked and rapid vacuolization after the use of large doses of members of this series (particularly urethan, Sollmann and Brown, 1902).

Blood absorbs considerably more chloroform than does salt solution. This excess cannot be removed by a vacuum.

The cells of other organs of the body also suffer, especially with chloroform and when the anesthesia is prolonged.

The patient remains in a general apathetic condition and dies inside of several days with the general phenomena of heart failure. The autopsy in such cases reveals fatty degeneration throughout the body, and especially in the liver and heart. Recent researches make it appear that these fatty degenerations are not the dangerous element. They appear quite easily, but disappear again equally readily. The real danger seems to be in *degenerative changes in the cardiac ganglia.* These are cumulative and persistent. They are seen after chloroform, chloral, morphin, and large doses of atropin, but not after ether. They seem especially dangerous in the "status lymphaticus" (Strassmann, 1898).

If ether is taken into the stomach, it is rapidly volatilized and distends the organ, sometimes so much as to interfere with respiration; it may even produce rupture of the organ. It also causes considerable local irritation, and consequently a temporary leucocytosis. Anesthesia may be produced in animals by the gastric administration of chloroform (Gréhant, 1905, see Index).

IV. OTHER GENERAL ANESTHETICS.

The slow action of ether and the dangers of chloroform have led to the trial of a number of other general anesthetics. Schneiderlin has proposed a narcosis by morphin and atropin. In laboratories, a general anesthesia is induced in animals by urethane, chloral, and chloretone. All these methods have the drawback that the degree of anesthesia cannot be adjusted to the varying needs of the case. Inhalation anesthesia cannot be replaced by them.

Of the varying substitutes which have been suggested, nitrous oxid alone has thus far firmly established its value. It is discussed in the following chapter. Ethyl chlorid is promising, but is still in the experimental stage. Ethyl bromid and methyl oxid have not stood the test of continued use. Anesthetic mixtures are to be condemned. The problem has been partly solved by the introduction of combination anesthesia; *i. e.,* the preliminary use of a quickly acting anesthetic, followed by ether.

Ethyl Chlorid (C_2H_5Cl) has proven very useful for short anesthesia, as in minor surgery; or to precede the administration of ether or chloroform. When it is administered for a short time only, it seems quite safe; but with prolonged administration it produces the same effects as chloroform (E. D. Brown and Gebauer, 1905), and seems to be even more dangerous.

Its main advantages consist in the rapidity with which anesthesia is induced; in the consequent absence of struggling, excitement, and unpleasant sensation; in the very prompt and complete recovery, with a minimum of after-effects. The muscular relaxation and abolition of reflexes are incomplete, and a little experience is required to recognize the proper time for operating. It has occasionally failed in alcoholic patients.

It may be administered by spraying it on a chloroform mask. This method is so wasteful that a special mask is to be preferred, allowing its administration in gas form, and restricting the admission of air. It has also been used by pouring a small amount into a closed mask. These methods utilize a partial asphyxia; they consume from 5 to 10 c. c. for short operations (Large, 1906).

Ethyl Bromid (C_2H_5Br) resembles the ethyl chlorid in most respects. However, it must not be pushed to the disappearance of reflexes, since the respiration is paralyzed about the same time. The zone of safety is therefor very narrow. Pain is abolished before consciousness, and the operation must be made before consciousness is entirely gone. The proper time for operating is somewhat difficult to choose, and the drug is very dangerous in unskilled hands. With experience, the danger seems to be slight. The proper amount (for adults, 8 c. c.; for children not more than 1 c. c. per year) is poured on a folded towel or cone, and administered to the exclusion of air, until the proper degree of anesthesia is reached. It is then removed. It is only suitable for short operations (tonsilotomy, etc.). The administration requires 20 to 40 seconds; the anesthesia lasts about two minutes. Recovery occurs at once.

After a bottle has been opened, the contents cannot be used again, as they deteriorate rapidly. The drug must not be confused with *Ethylen bromid* ($C_2H_4Cl_2$), which is very poisonous.

Bromoform ($CHBr_3$) is not sufficiently volatile to be of use as an anesthetic. It is employed as an antispasmodic in whooping cough.

Anesthetic Mixtures.— The attempts to blend the actions of anesthetics by mixing them have been uniformly unsuccessful, because the ingredients do not volatilize with equal rapidity. The composition of the inspired anesthetic is therefore absolutely uncertain. As a rule, the concentration of the chloroform increases during the anesthesia. These mixtures are therefore quite as dangerous as chlorofrom, and should be condemned (Kochmann, 1903).

A. C. E. Mixtures.— These contain alcohol, chloroform, and ether in various proportions. (The English mixture = 1 : 2 : 3; Billroth's = 1 : 3 : 1.) Their effects correspond to those of chloroform, of uncertain dilution. They lower the blood pressure.

Other Mixtures.— *Schleich* believes that it would be an advantage to employ anesthetics whose boiling point lies at the temperature of the body. For if the boiling point is lower (*e. g.*, with ether), the vapor will expand, oppose a greater pressure to the excretion of CO_2 and induce asphyxia. If, on the other hand, the boiling point lies above the body temperature, some of the vapor will be condensed, the excreted air will contain less than the inhaled air, and there will be danger from the drug (as with chloroform). This is based on fallacious *à priori* reasoning; but even were it true, it may be doubted whether the boiling point has this great importance in practice, since the anesthetic is not inhaled automatically, but is controlled according to the symptoms. Schleich secured an anesthetic of the boiling point of about 40° C. by mixing ether, chloroform, and petroleum ether, the last for the purpose of lowering the boiling point. A mixture of ether, chloroform, and ethyl chlorid, boiling at 40° C., has recently been recommended under the name of *anesthol*, with the claim that it is a chemic compound, and that its composition does not alter on evaporation. The claim seems to be unfounded. Other mixtures, containing ethyl bromid, etc., have also found advocates (Schleich).

Combined Anesthesia.— To avoid the prolonged excitement stage of ether, with the disagreeable sensation of suffocation, and the dangers of struggling in atheroma or heart disease, it has been customary in certain cases to start the anesthesia with chloroform, changing to ether as soon as the anesthetic stage is reached. The practice is objectionable, on account of the dangers of chloroform in the first and second stages. A notable advance was made by using the inhalation of nitrous oxid (mixed with about 2% of oxygen) for the production of the primary anesthesia. This has been entirely successful, and is used as a routine in some hospitals. The expense of the apparatus and gas is the only objection. More recently, ethyl chlorid has been substituted. In either case, the anesthesia during prolonged administration is maintained with ether.

Volatile Narcotics of Toxicologic Interest.— Gasolin.— (*Petroleum Benzin.*)— The more volatile products of petroleum, administered in the form of concentrated vapor, cause purely paralytic symptoms in frogs, but in mammals they seem to have only a weak anesthetic action. If they are inhaled to the exclusion of air, they will cause an asphyxial anesthesia. Before this sets in there are very characteristic convulsions (Sollmann, 1904). The animal struggles violently, then falls on its side and claws the air with all fours, as if running. The pupils are widely dilated. Reflexes absent. The spasms are intermittent, and between them the dog is perfectly limp, except that the toes, tail, and eyelids continue to twitch. The respiration is first stimulated, then weakened. There is a paralysis of the vagus, then a depression of the cardiac muscle, and later of the vasomotor center. Either heart or respiration may stop first.

(*Benzol* shows similar changes.)

These liquids are therefore unsuitable as anesthetics, even for animals. Gasolin is said to be used as an *intoxicant.*

When *petroleum* is swallowed, it produces narcotic effects similar to those of alcohol, with strong gastroenteritis. It is toxic in proportion to its content of the more volatile products. No fatal case has thus far been reported. Coal oil applied to the skin is a moderate irritant, and may lead to dermatitis (Joseph, 1896).

Carbon Disulphid (CS_2).—This very volatile fluid has a toxicologic importance, from its extensive use in the arts, particularly in the rubber industry (Stadelmann, 1896).

Acute Poisoning is quite rare and produces effects similar to those of chloroform.

Chronic Poisoning is the more common. The symptoms may not appear for several weeks and then develop quite slowly so that several stages may be distinguished. The effects have a pathological basis in irritative changes throughout the body. The symptoms begin with disturbed sensation (headache, formication, vertigo, etc.) and gastro-intestinal catarrh. In the second stage there is irritability, excitement, hysterial manifestations, etc., and signs of marasmus. The third stage shows central paralytic, or epileptic features, and peripheral neurites. Ataxia has been reported. The marasmus is pronounced. Degenerative *histologic changes* are found in blood (hemolysis, leucocytosis, anemia; no methemoglobin formation), nerve cells and dendrites, liver (vacuolization), kidneys, and lungs. Death does not occur until very late. (A more extensive description is given on page 461 of the first edition.)

V. THE CHOICE OF THE ANESTHETIC.

For short operations the preference should be given to local anesthesia; or where this is not practicable, to nitrous oxid or ethyl chlorid.[1]

For *prolonged operations* the choice is practically restricted to ether and chloroform. There can be no doubt of the *much greater safety of ether;* the average fatality with ether being about 1 in 12,000; that of chloroform 1 in 3,000. *Ether should therefore be preferred, unless it is specifically contraindicated.*

These *contraindications* to ether are the following:

It is more disagreeable to take. The struggling contraindicates the drug in atheroma. These objections are largely met by the combined methods. Ether is to be avoided in all diseases of the respiratory organs. The relative damage to the kidneys by the two anesthetics is disputed. (Both should be avoided in advanced renal or cardiac disease. Chloroform should never be used when the heart is abnormal, nor when the operation is likely to lead to much hemorrhage. It is preferred, on the other hand, in brain surgery.) Ether does not cause as complete muscular relaxation, and chloroform is preferred when this is essential. Ether anesthesia being less lasting, chloroform is preferred when the inhalation has to be interrupted; as, for instance, in operations about the mouth. The inflammability of ether forbids its use when the cautery is to be employed, and enjoins great caution when open fires or lights are in the room. The greater volatility of ether limits its usefulness in hot climates; its slower action and the larger bulk which is required also make it less useful on the battlefield.

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[1] A quick and short anesthesia can also be produced by ether, the so-called "one minute anesthesia." A teaspoonful is poured into the cone, and the patient is directed to take deep inspiraions, whilst counting. The operation is made as soon as the counting becomes irregular. The method cannot compare with those given in the text.

Chloroform is especially contraindicated in prolonged operations, on account of the late degenerations.

Occasionally, the choice of the anesthetic is determined by the idiosyncrasy of the patient.

VI. PRACTICAL RULES FOR ANESTHESIA.

Preparations.— Before commencing the administration, the patient should be prepared by receiving a cathartic on the previous day, and nothing but a very light meal for at least two hours before the anesthesia, to prevent the discharge of the contents of the alimentary canal during the anesthesia. He should be carefully examined for cardiac, renal, and pulmonary disease. He should then be placed in such a position as to interfere to the smallest possible extent with respiration; the *head preferably low.* The clothing should be loosened and all foreign bodies — false teeth, etc.— removed from the mouth. All the instruments, etc., apt to be used should be at hand before the administration is started — both anesthetics, mask, hypodermic with strychnin, brandy, etc.

It is very useful to administer a hypodermic injection of morphin (10 mg. = ⅙ grain) and atropin or hyoscin (0.5 mg. = 1/120 grain) about half an hour before the anesthetic is started.

The morphin lessens the apprehension of the patient, and the struggling and excitement. It renders the course of the anesthesia much smoother, and reduces materially the quantity of anesthetic which has to be administered; and thereby, the dangers of the after-effects. The atropin or hyoscin reinforce the narcotic action of the morphin somewhat; but they are especially useful by preventing the hypersecretion of mucus, and the reflex vagus stoppage of heart and respiration. This may also be attained by cocainizing the nasal mucosa. It must be remembered that these alkaloids affect the pupil, so that this cannot what; but they are especially useful by preventing the hypersecretion be utilized as a danger signal. A small dose of strychnin is also useful, if respiratory failure is to be feared.

To prevent the local action of the anesthetic on the face, it is well to anoint the mouth and nose with petrolatum. Care should be taken to have the patient close his eyes.

In regard to the **administration of the anesthetic** itself: This is usually done by *inhalation,* since the amount can be much more readily regulated in that manner. Attention should be directed to the following points:

The *concentration of the vapor.* It must be well understood that the immediate danger lies in the concentration of the anesthetic vapor, and not in the actual amount employed. The absolute quantity is only important in connection with the after-effects. With regard to this concentration, experiments have shown that the percentage of ether in the respired air must be 3.6 vol.; of chloroform, 1.0 to 1.5 vol. These limits are quite safe, and such quantitative mixtures have, indeed, been given by special *apparatus.* Aside from the cumbersome nature of the latter, an important objection to such standard mixtures is the slowness with which they produce anesthesia. It is certain that much stronger mixtures than these may be borne for a short time, and are quite safe in starting the anesthetic. Nor have any of these apparatus deserved or attained much popularity.[1]

The fact is that no mechanical device can replace the sense of responsibility, the constant watchfulness, and the quick reasoning of the experienced anesthetizer. Anesthetization is not a physical experiment where the factors can all be foreseen, but the condition of the patient is apt to vary from moment to moment, and must be taken into account. The state of the respiration must be carefully watched: if the patient holds his breath, the mask must be held farther away, since the next respiration will be an especially deep one. When the respiration becomes slow and shallow, this signifies that a sufficient amount has been taken, and that the quantity may be lessened. The object is to give no more than is necessary to just keep the patient anesthetized. On the other hand, care must be taken to keep him thoroughly under the influence, for shock is much more common under partial anesthesia. Since the respiration and circulation react one upon the other, so that no change could occur in the latter without being noticed in the former, and since most accidents occur from stoppage of the respiration, it may be sufficient to watch this alone, as is advised by some. But as it is of the highest importance to discover beginning failure of the one or the other at the earliest possible moment, the anesthetizer cannot be considered as doing his duty unless he carefully observes both. The argument that watching the circulation distracts the attention from the respiration should not hold; the anesthetizer should be able to keep his attention fixed upon both.

The fact that the required concentration of ether is much greater than with chloroform, leads to the temptation not to admit sufficient air. This must be carefully guarded against, or asphyxial symptoms may result simply from a deficient supply of oxygen.

Chloroform is given on a cloth, held some little distance from the face, and best supported on a frame. With either anesthetic the mask should at first be kept fairly away from the mouth, until some narcotic effect is obtained, to lessen the feeling of choking from the concentrated vapor. The patient should be encouraged to breathe quietly and regularly. Counting is a good expedient for this purpose. With regard to the chloroform, this is best dropped in a regular manner on the cloth. The rate should under no circumstances exceed 60 per minute, and usually should not be over 12. After the anesthetic stage has been induced 6 drops per minute will usually suffice. This will be found better than to remove the mask altogether and reapply it with a larger dose when the patient shows signs of recovery.

Ether is usually administered on a special mask, which admits only a limited amount of air. About a tablespoonful is placed in the mask, and repeated as needed.

It may also be given by a "drop method," being dropped at the rate of about 150 per minute over the entire surface of a chloroform inhaler with about 8 layers of gauze, held an inch from the face. This wastes considerable ether, but avoids largely the suffocation, cyanosis, and struggling of the first and second stage.

The **quantity of anesthetic** which is required for an ordinary operation is very variable. Some 40 c. c. of chloroform, or 150 c. c. of ether, by the ordinary method, or 250 c. c. by the drop method, are about the smallest quantities for an hour's anesthesia.

The *tongue* may fall back and interfere with respiration, as denoted by noisy breathing. In this case it will usually suffice to push the jaw forward, but it may be necessary to draw out the tongue. If much *mucus* accumulates, this should be removed with a cloth. If *vomiting* occurs, the head should be turned to the side.

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[1] The simplest form is that proposed by A. V. Harcourt: Suppl. Brit. Med. Journ. 1903, p. 143.

If the symptoms of the fourth stage (p. 428) should make their appearance, or if either heart or respiration should show signs of failing, the anesthetic should at once be withdrawn and **restorative measures**[1] started. These consist in lowering the head of the patient, in order to give the medullary centers the benefit of any circulation still remaining. A few rhythmic compressions of the epigastrium may be tried, but if these do not succeed quickly, artificial respiration by any of the methods should be begun at once. This prevents asphyxia and eliminates the poison. The cardiac region should also be compressed strongly at the rate of seventy times per minute, since this aids the action of the heart and supplies a mechanical stimulus. A venesection is sometimes efficient in starting the heart, but is always risky. *Faradisation* of the phrenic nerve or of the heart has also been advocated, but appears to be prompted more by the desire to do something than by any rational view of the object to be accomplished. Stimulation of the phrenic, to be sure, causes contraction of the diaphragm and inspiration, and if done intermittently, would take the place of artificial respiration. But it possesses no advantage over the latter, and besides the fact that the time required to adjust the apparatus might be much better utilized, there is apt to be stimulation of the vagus — a most undesirable feature.

With regard to faradization of the heart, there is no more effectual way known of killing this organ than electric stimulation (by the production of delirium cordis), and the only reason why more harm has not been done by this senseless procedure is that the electricity, as it is ordinarily applied, does not penetrate through the chest walls.

Of drugs, strychnin, or caffein, by virtue of the stimulation of the respiratory and vasomotor centers, are very useful if given in time — *i. e.,* while they may still be absorbed. Injection of normal salt solution may be tried.

The *inhalation of oxygen* is also very useful. This does not decompose the chloroform, but counteracts the asphyxia. It has been suggested that oxygen be administered throughout the course of the anesthesia. This requires special apparatus.

One of the best methods of resuscitating animals is by strong sensory stimulation, as of the sciatic. Hypodermic injections of ether, which have been used in man, might be supposed to act in the same manner. But clinical observers condemn their use, and experiments on animals show that the stimulus is too weak to produce much effect. Small doses cause no perceptible change in blood pressure or heart rate, whilst larger doses produce narcosis with fall of blood pressure. The respiration, however, may be materially improved (Fig. 82 *B*).

The inhalation of ammonia is sometimes remarkably effective.

It is often necessary to keep patients lightly under the influence of an anesthetic when no skilled assistant is available, as in obstetric practice. Here a method of **self-inhalation** suggested by Brunton is very useful:

The inside of a tumbler is covered with blotting-paper. A few drops of chloroform are poured on, and this is given to the patient, with directions to hold it an inch from his mouth and inhale. This works automatically, for as the patient becomes narcotized he naturally allows his hand to drop, and so removes the tumbler; and as soon as he becomes conscious and sensitive to pain, he will replace it. It would not, of course, be possible to induce deep anesthesia in this manner.

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[1] Exercise 58.

Other Uses of Anesthetics.— Besides the use of anesthetics in operation, they are often used in *obstetrics,* especially chloroform. Not complete anesthesia, but merely a dulling of the pain, is desired here, and the dose should be small, since larger quantities are apt to prolong the labor, and may be dangerous to the fetus by lowering the general blood pressure. Clinicians insist that anesthetics are remarkably well borne during labor. This has not been explained.

A light chloroform anesthesia is also used to dull the excitability of the central nervous system, in *pain* or *insomnia;* and to *check convulsions,* as those of strychnin, tetanus, or eclampsia. It is especially useful in the onset of these conditions: when the convulsions are fully developed it must be used cautiously, to avoid asphyxia.

For the production of the light anesthesia, chloroform is preferred to ether, since it can be more easily regulated, and its effects are more lasting.

A very deep degree of anesthesia is employed in *reducing dislocations,* to relax the tone of the opposing muscles.

Besides the narcotic action, the *local irritation* of these drugs is used therapeutically in the same manner as alcohol, chloroform being a very active rubefacient and much superior to ether, since the latter evaporates too quickly. The use of chloroform as anthelmintic and of ether for freezing is discussed elsewhere (Chapter XXX, F). Bromoform is given in whooping-cough.

VII. MATERIA MEDICA.

Chloroformum (U. S. P., B. P.).[1]—*Chloroform.*— Contains at least 99% $CHCl_3$, made by distilling alcohol with chlorinated lime and purifying the product. Sp. Gr. 1.49. Soluble in 200 parts of water and in all proportions of alcohol or ether. Boiling-point, 60° to 61° C. Not inflammable. *Dose:* 0.1 to 1 c. c. (2 to 15 minims) (0.3 c. c. = 5 ♏., U. S. P.).

Preparations:

Aqua Chloroformi (U. S. P., B. P.).— A saturated solution in water. (Made by agitation.) Flavoring and hypnotic. *Dose:* 4 to 15 c. c. (1 to 4 drachms) (16 c. c. = 4 ʒ, U. S. P.).

Emulsum Chloroformi (U. S. P.).— A 4% emulsion. *Dose:* 8 c. c. = 2 ʒ, U. S. P.

Spiritus Chloroformi (U. S. P., B. P.).— A 6% solution. *Dose:* 2 to 4 c. c. (½ to 1 drachm) (2 c. c. = 30 ♏., U. S. P.).

Linimentum Chloroformi.— 30% with soap liniment, U. S. P. [50% with camphor liniment, B. P.].

*_Mistura Chloroformi et Cannabis Indicæ Composita_, N. F.— Each teaspoonful contains 0.5 c. c. each Chloroform and Tr. Cannabis Indica; 0.25 c. c. Tr. Capsicum; and 0.01 Gm. Morphin Sulphate.

Tinctura Chloroformi et Morphinæ Composita (B. P.).— 7.5% chloroform; 1% of Morphin Hydrochlor., and 5% of Dilute Hydrocyanic Acid; also Capsicum, Peppermint, and Cannabis Indica.

Bromoformum (U. S. P.).— $CHBr_3$. A heavy liquid, resembling chloroform. Sparingly sol. in water, readily in alc. or ether. Sp. Gr. 2.808. Boiling-point, 148° C. *Dose:* 0.05 to 0.4 c. c. (1 to 5 ♏.) (0.2 c. c. = 3 ♏., U. S. P.) in mixtures of alcohol and glycerin, or dropped on sugar, not as emulsion.

Æthylis Chloridum (U. S. P.).— *Ethyl Chlorid.*— C_2H_5Cl. Prepared by the action of HCl on absolute alcohol. Colorless, extremely volatile liquid, of sharp, sweet taste, and peculiar odor. Inflammable. Sp. Gr. 0.918 at 8° C. Boiling-point, 12.5 to 13° C. Sparingly sol. in water, readily in alc. or ether. Dispensed in special glass or metal tubes. Used for freezing and for general anesthesia.

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[1] See purity tests, Exercise 10.

* Not official.

* **Ethyl Bromid,** C_2H_5Br. General properties resemble the preceding. Boiling-point, 38 to 40° C.; Sp. Gr. 1.45 to 1.47. Should be protected from light and heat. Used for short general anesthesia.

* *Chlor-methyl-menthyl ether,* used by inhalation, has been recommended against coryza.

Æther (U. S. P.).[1]—*Sulphuric Ether, Ethyl Oxid.*—Contains 96% by weight of $(C_2H_5)_2O$; made by acting on alcohol with strong sulphuric acid, distilling, and purifying the product. End-reaction = $2C_2H_5OH + H_2SO_4 = (C_2H_5)_2O + H_2O + H_2SO_4$. Sp. Gr. 0.716 to 0.717; boils at 35.5° C. Inflammable. Soluble in 10 vol. of water, all proportions of alc., etc. *Dose:* 1 c. c. = 15 ♏, U. S. P.

This is the *Æther Purificatus* (B. P.). *Æther* (B. P.) is a less pure and more watery Ether.

Preparations:

Spiritus Ætheris (1/3 Ether, 2/3 Alcohol, U. S. P.) [1/10 Ether, 9/10 Alcohol, B. P.].—*Dose:* 1 to 4 c. c. (1/4 to 1 drachm) (4 c. c. = 1 ʒ, U. S. P.).

Spiritus Ætheris Compositus (U. S. P., B. P.).—"Hoffmann's Anodyne."—Above with 2.5% of "Ethereal Oil." *Dose:* same.

Æther Aceticus (U. S. P., B. P.).—$C_2H_5.C_2H_3O_2$. Boiling-point, 72° C. Soluble in 7 parts water, freely in alc., etc. *Dose:* 1 c. c. = 15 ♏, U. S. P.

Acetonum (U. S. P.).—$CH_3.CO.CH_3$. Boiling-point, 56.5° C. Solvent for fats, resins, rubber, camphor, gun-cotton, etc. Sp. Gr. 0.790. It is faintly hypnotic, but causes so much dyspnea that it is not used internally (Albertoni, 1884).

Benzinum (U. S. P.) and *Benzinum Purificatum* (U. S. P.).—*Petroleum Benzin.*—Hydrocarbons, chiefly of the methane series (C_5H_{12}, C_6H_{14}, etc.). Sp. Gr. 0.638 to 0.660° C. Boiling-point, 45 to 60° C. Insol. in water, sol. in 6 alc. Highly inflammable.

(D) GROUP OF HYDROCARBON HYPNOTICS.

All the members of the Hydrocarbon Group tend, in small doses, to produce sleep. But many have properties which prevent their being used for this purpose. Thus, chloroform and ether are too irritant to the stomach and later to other organs; and being rapidly absorbed and excreted, their action is not sufficiently lasting. Further, the preceding stimulation is not desirable.

A really desirable hypnotic of this series must combine the following characters to the highest degree attainable:

Its action must be quick and lasting. Very volatile substances are therefore excluded. It must produce the maximum hypnotic action, with the least depression of the medullary centers. It must not possess an odor or taste which would preclude its employment; and it must not irritate the stomach. Preparations which are insoluble in water, but which are nevertheless absorbed, are valuable because they are nearly tasteless, and because their action is apt to be more lasting. A soluble compound which could be used hypodermically would be very useful, but has not yet been invented.

Study Materia Medica Lesson 32.

* Not official.

A chemico-physiological *classification* of the hydrocarbon narcotics is the most satisfactory. They may be classed as:

I. Chlorin substitution products.
II. Ethyl derivatives.
III. Aldehydes and Ketones.

None of the products so far invented satisfy all the demands formulated above. The chlorin compounds are the most powerful, but also the most toxic. The ethyl derivatives are safe, but comparatively weak. The aldehydes and ketones are inferior in every respect. A choice must therefore be made according to conditions: The ethyl derivatives, especially Trional, are most generally useful. But if a very strong hypnotic is necessary, chloral or chloralose must be employed.

I. CHLORIN DERIVATIVES.

These owe their activity to the entrance of chlorin atoms into the molecule. The oldest, and still the most widely used, of these compounds is *chloral hydrate*. In the endeavor to obviate the undesirable features of chloral, various modifications have been suggested. It was found, however, that these acted only by virtue of the regeneration of chloral within the body. The comparative insolubility of some of these compounds avoids the bad taste and the gastric irritation, but at the same time it reduces their hypnotic power. They therefore lose entirely the one desirable feature of chloral — its great activity; and are in every other respect inferior to the less dangerous ethyl derivatives.

Chloral Hydrate.— This is chemically trichloraldehyd:

$$\underset{= \text{Ethyl Aldehyd}}{CH_3.COH} \qquad \underset{= \text{Chloral.}}{CCl_3.COH} \qquad \underset{= \text{Chloral Hydrate.}}{CCl_3.COH.H_2O}$$

This substance was discovered by Liebig in 1831 and introduced as a hypnotic by Liebreich in 1868. He assumed that it was decomposed in the organism, as it is by the action of alkalies in the test-tube:

$$\underset{\text{Chloral.}}{CCl_3.COH} + KOH = \underset{\text{Chloroform.}}{CHCl_3} + \underset{\text{Pot. Formate.}}{KCO_2H}$$

This is not the case, the chloral being excreted for the most part as trichlorethyl-glycuronic acid. This latter reduces Fehling's solution, which gave rise to the erroneous assertion that chloral causes glycosuria. A small portion of the chloral is excreted unchanged, whilst a fraction is decomposed, being excreted as chlorids.

Action.— This occurs along the same lines as with the whole hydrocarbon series: *depression,* first of the brain, then of the spinal cord, and lastly of the medulla; and, finally, a direct action upon the heart muscle. The action is developed much more slowly, however, than with the fluid members of the series. With **small doses** it is quite possible to confine it purely to the brain, resulting in a lessened receptivity, and a lowering of the mental activity, and in this way producing sleep — for the most part indirectly by the cutting off of afferent impulses. This resembles the *natural sleep* in every particular — as in the latter, the respiration and pulse are slowed, but not more than with normal sleep.

Somewhat larger doses[1] cause a deeper sleep, with lessening of the spinal reflexes; and as the dose is increased, the depression of the medulla makes itself felt by *slowing of the respiration* and *fall of blood pressure*. The vasomotor paralysis is so prominent that chloral is often used in the laboratory to secure paralysis of this center. The pulse is also slowed through a direct action on the cardiac muscle. The action on the *isolated heart* is precisely as with chloroform: a lessened rate and amplitude, sometimes preceded by a short increase due to direct irritation. As in the case of chloroform, it is impossible to state to what extent the vasomotor and the cardiac paralysis respectively are concerned in the fall of blood pressure. A *dilatation of the cutaneous* vessels is quite a marked feature and may lead to the appearance of skin eruptions. Larger doses always cause a marked *fall of temperature* on account of this cutaneous vasodilatation coupled with the diminished production of heat from lessened movement (and perhaps lessened irritability of the heat-regulating centers?). In *fatal doses* death is ordinarily caused by paralysis of the respiratory center, although it may take place by paralysis of a weakened heart, just as in the case of chloroform. On this account, and because it is apt to induce the same degeneration of organs, it is contraindicated in the same conditions as chloroform — degeneration of heart or vessels, nephritis, etc.; also in lowered activity of the respiratory center.

The action of chloral upon *metabolism* consists in an increased destruction of proteids, the waste products being excreted in a less completely oxidized condition than is the case normally.

The *local action* of chloral is so pronounced as to allow of its use as a rubefacient. Its action on the stomach is consequently very prominent, and it must be largely diluted with water before administration; else it may produce vomiting. In any case, large doses are apt to show after-effects, referable to a gastritis.

Chronic chloralism is a condition of no great rarity. It produces the same degenerations, moral and physical, as does alcohol.

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[1] Exercise 29.

Chloralum Hydratum (U. S. P.) [Chloral Hydras, B.P.] (*Chloral*).— $CCl_3COH + H_2O$. Prepared by acting on alcohol with chlorin and purifying the product. Colorless crystals, freely soluble in water, alcohol, and ether. *Dose:* 0.3 to 1.5 Gm. (maximal dose, 3 Gm.) (5 to 25 grains). Largely diluted. (1 Gm. = 15 grs., U. S. P.)

Syrupus Chloral (B. P.).— One drachm = 10 grains of chloral. *Dose:* ½ to 2 drachms.

* *Chloralum Camphoratum,* N. F.— A liquid composed of equal parts of camphor and chloral. For external use.

* *Mistura Chlorali et Potassii Bromidi,* N. F.— Each teaspoonful contains 1 Gm. (15 grs.) each chloral and Pot. Bromid, and 8 mg. (⅛ grain) each of Ext. Cannabis Indica and Ext. Hyoscyamus.

* *Meta-Chloral.*— A polymer; insoluble, odorless, and almost tasteless; hypnotic power weak, short, and uncertain. *Dose:* 1.5 to 2 Gms. (20 to 30 grains).

Butyl Chloral Hydrate (B. P.) (*Croton Chloral Hydrate*).— Soluble in 50 parts of water, freely in alcohol or glycerin. Hypnotic action powerful, but short; great gastric irritation; claimed to be potent in trigeminal neuralgia. *Dose:* 0.3 to 1 Gm. (5 to 15 grains).

* *Chloralimid.*— $CCl_3 - CH = NH$; a very stable compound, insoluble in water; has not been tried sufficiently. *Dose:* 1 to 3 Gm. (15 to 45 grains).

Chloralformamidum (U. S. P.).— (*Chloralamid.*)— $CCl_3.CH(OH)\text{-}NH.COH$. Colorless, lustrous crystals, sol. in 18.5 parts of water, 1.3 alc. Aqueous or acid solutions quite stable at ordinary temperature, partly decomposed at 60° C., or by alkalies into chloral hydrate and ammonium formate. Feebly bitter taste. Hypnotic action weaker than chloral, but the cardiac, medullary, and local action is also much weaker. Even a 10% solution is said to be not irritant to the eye. The lesser depressant effect on circulation and respiration is due to the stimulant action of the liberated formamid ($CHONH_2$) (Friedlander, 1893).

This compound cannot replace chloral as an analgesic, or in delirium; but it is an efficient hypnotic, and has also been recommended in seasickness (combined with bromids). *Dose:* 0.6 to 4 Gms. (10 to 60 grains), usually 2 Gms. (1 Gm. = 15 grs., U. S. P.); in brandy or elixir.

* *Acetone-Chloroform* (Chloretone, trichlormethyl propanol).— $CCl_3C(CH_3)_2OH$. Colorless crystals of camphoraceous odor; sparingly soluble in water (125 parts), readily in alcohol. Best given in capsules or tablets. *Dose:* to 1 Gm. (15 grains).

In the doses in which it is used it has no action on circulation or respiration, and is not dangerous in even much larger doses. But its effect is also not so very strong. Really narcotic doses are even more dangerous than chloral.

Death results from respiratory paralysis, with simultaneous central vasomotor paralysis and cardiac depression — the latter, however, not as pronounced as in the case of chloral. There is also an effect upon metabolism, which finds expression in a great lowering of temperature and diminution of oxygen consumption, and the animal often shows marasmus when the acute effects have passed off (Impens, 1901).

Chloretone is a valuable ***anesthetic for laboratory animals,*** as it allows of long operations without requiring any attention. The dogs are given the usual dose of morphin (see dose table). As soon as vomiting has occurred, 0.2 Gm. of chloretone per Kilogram of animal, is administered by stomach tube. The chloretone is previously dissolved in the smallest possible amount of alcohol. The anesthesia is complete in 15 to 20 minutes, and lasts several hours. The blood pressure falls rapidly in rabbits, slowly in dogs. Chloretone is inadvisable when it is wished to have the animal recover.

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* Not official.
Study Materia Medica Lesson 33.

* *Chloralose.*— Freely soluble in hot water. *Dose:* 0.3 to 0.5 Gm. (5 to 8 grains). Best in capsules. A condensation product of chloral and glucose. The opinions as to its value vary. Some observers consider it as strongly hypnotic as chloral and devoid of the medullary depression. Others have seen very toxic effects, due to the presence of parachloralose (Henriot and Richet).

* *Dormiol.*— A condensation product of chloral and amylen hydrate. The hypnotic action is about equivalent to chloral, with less local irritation. Colorless fluid, camphoraceous odor, not unpleasant, pungent taste. Miscible with alcohol; slowly soluble in water. *Dose:* 15 c.c. of the 10% solution (= 1.5 Gm.) in syrup.

* *Caffein chloral* and * *Chloral urethane* have no advantage over mixtures of the active constituents.

* *Hypnal* is a compound of chloral and antipyrin, and combines the actions of both.

* *Somnal* is not a chemic compound, but a mixture of chloral, alcohol, and urethane.

III. ETHYL DERIVATIVES.

The radicle C_2H_5 has strong hypnotic properties when it is combined in such a way that it can exert its action. This effect is indicated in ethyl alcohol, but this as well as many other ethyl compounds are oxidized too rapidly to be available as hypnotics. The ethyl must be protected from oxidation; this is accomplished in the urethane and sulfonal molecules. The hypnotic, and especially the analgesic, effects of the ethyl compound is always weaker than those of chloral; but on the other hand, ordinary doses lack any appreciable action on circulation and respiration. *Toxic doses* cause collapse, rapid cooling, and damage to cardiac muscle.

Æthylis Carbamas (U. S. P.).— (*Urethane.*) — $CO(OC_2H_5)NH_2$. An ester of carbamic acid, obtained by the reaction of alcohol on urea. Colorless, odorless crystals, of saline taste. Sol. in 1 water, 0.6 alc. *Dose:* to 4 Gms. (1 ʒ) (1 Gm. = 15 grs., U. S. P.). It is a very good and harmless hypnotic, but not very strong, and patients soon become immune to it. It has quite a decided diuretic action. It lowers the excretion of nitrogen and sulphur, even in doses as small as ⅓ Gm., whilst the phosphorus is increased. Large doses cause in rabbits a vacuolar degeneration of the hepatic epithelium. It is excreted as urea (Schmiedeberg).

* *Hedonal* (methyl-propyl-carbinol-urethane) is more hypnotic, but also more toxic, and diuretic, than urethane. White powder, almost insoluble in water, soluble in alcohol. *Dose:* to 2 Gms., best in powders or capsules (Heichelheim, 1900).

* *Veronal* (diethyl-malonyl-urea) has been highly recommended. It is a white crystalline powder, of faintly bitter taste. Sol. in 150 water. *Dose:* 0.3 to 1 Gm. (5 to 15 grs.), in capsule or in hot milk. Habit has been reported (Krep, 1905).

Sulfonal, Trional, and Tetronal.—

$(CH_3)_2C(SO_2.C_2H_5)_2$ = Sulfonal (Sulphonmethanum)
$CH_3.C_2H_5.C(SO_2.C_2H_5)_2$ = Trional (Sulphonethylmethanum)
$(C_2H_5)_2C.(SO_2C_2H_5)_2$ = Tetronal

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* Not official.

These three resemble each other very closely in their action. Since Trional is the more soluble, more quickly absorbed, and more active, it is now preferred.

They are less dangerous than chloral, but do not act as strongly on pain, and if used for the latter, must be supplemented by Morphin (Kast, 1888).

Their excretion seems to be slower than their absorption, so that there is a tendency to a cumulative action. This leads to gastritis, renal disease, and ill-understood changes in the blood resulting in hematoporphyrinuria. The latter has so far been produced only in man and in rabbits. These phenomena can be avoided by intermitting the administration at times. The factor urea ÷ nitrogen is lessened. The fate of sulfonal in the organism is not known.

Sulphonal habit has been reported.

Quite a number of fatal cases of acute *sulphonal-poisoning* are on record. The prominent symptoms were: Various forms of paralysis, often of wide extent — rarely spasms; various cutaneous eruptions; gastro-intestinal disturbance and extreme constipation; cardiac and respiratory weakness with a peculiar dyspnea; somnolence or insomnia, frequently with mental disorder. Hematoporphyrinuria is not always seen in acute cases. The autopsy is generally negative (Taylor and Sailer, 1900).

Sulphonmethanum (U. S. P.) [*Sulfonal,* B. P.].— Colorless crystals, odorless and tasteless. Sol. in 360 water, 47 alc., 15 boiling water. *Dose:* to 2 Gm. (30 grs.) (1 Gm. = 15 grs., U. S. P.). Best as powders.

Sulphonethylmethanum (U. S. P.).— (*Trional.*) — Colorless, odorless crystals, bitter taste. Sol. in 195 water, more readily in boiling water, readily in alc. *Dose:* as the preceding.

* *Tetronal.*— Properties and dose resemble the preceding.

III. ALDEHYDES AND KETONES.

These are inferior to the other groups in hypnotic power, whilst their toxic and irritant properties are more powerful than those of the ethyl derivatives.

Paraldehydum (U. S. P., B. P.).— $(CH_3.CHO)_3$; soluble in 8 parts of water, freely in alc. Especially objectionable for its very disagreeable taste, and for the persistent odor which it gives to the breath. *Dose:* 2 c. c. = 30 ♏. (U. S. P.), in brandy (Friedlander, 1893).

* ***Amylene Hydrate*** may be mentioned in this place. It is used as a hypnotic, and is claimed to lessen the polydipsia and polyuria of diabetes insipidus. Colorless fluid; soluble in 8 parts of water, readily in alcohol. *Dose:* 1 to 2 Gm. (15 to 30 grains), in glycerin, $2CH_3.C_2H_5.C.OH$ (Harnack and Meyer, 1894).

It will be useful to sum up at this point the principal remedies used for the production of sleep. They have received the name

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* Not official.

HYPNOTICS.

(*Synonyms.— Soporifics, Somnifacients; Narcotics,* if they produce depression of the psychic areas aside from their soporific effect; *Anodynes or Analgesics,* if they are especially active in relieving pain.)

The **indication** for the use of Hypnotics is insomnia, whether from excitement, pain, cough, nervousness, etc.

In the treatment of this condition it must be remembered that the drugs of this class act purely symptomatically; that they soon lose their effect; that none of them are entirely free from objection, be it through the tendency to the formation of drug-habit, through an irritant effect, or through the danger of overdosage. They should not, therefore, be resorted to except in case of necessity. The dose at the beginning should be very small — it must be remembered that in many cases the action of the hypnotic itself need not be very lasting, for sleep once induced tends of itself to continue. And this small dosage presents the opportunity of enlarging the dose when the patient becomes accustomed to it. When the hypnotics need to be continued for a long time, it is well to change frequently to a hypnotic of another type, to return to the first later. This obviates to a great extent the irritant effects and also the difficulty of the patient becoming accustomed to the drug.

It is the duty of the physician to inquire into the underlying condition; the removal of this frequently renders drugs unnecessary. If it depend upon worry, caffein, late eating, late hours, or want of exercise, these conditions should be removed. When it depends upon a preconceived idea of the patient that he cannot go to sleep, then a harmless powder of any kind will often have the desired effect. Other cases are due to a faulty circulation: anemia of the brain is sure to induce sleepiness, while congestion is apt to result in insomnia. When the tone of the blood-vessels is impaired, the effect of gravity in lying down may send an added supply of blood to the brain, and in this manner produce wakefulness. Drugs like digitalis would be of the greatest benefit in such conditions. Much may be done by drawing blood from the brain by applying warmth to the extremities and abdomen.

The Hypnotics may be classed, according to their clinical action, into the following types:

1. *Alcohol,* including beer and wines: there is a tendency to preceding excitement, but no dangerous depression. The hypnotic action is weak.

2. *Urethane, Hedonal, Trional, Paraldehyd:* These have a comparatively slow but lasting action. They are only to a slight extent analgesic, and depress reflexes less than chloral; but are, on the other hand, less dangerous; they must be considered intermediate in strength of action and in danger between alcohol and chloral.

3. *Chloral* possesses a quick and lasting action. With large doses, it is markedly anodyne and lowers reflexes, but is dangerous on account of depression of medulla. It is apt to produce gastric irritation.

Chloralose differs from chloral in heightening reflexes, and it has less action on the medulla.

4. *Aromatic Hypnotics.*— Lactophenin, acetphenetidin. The side-actions limit their value to febrile cases.

5. *Alkaloidal Narcotics:*

(*a*) *Morphin group:* Specifically against pain; heightens reflexes. Useful in cough.

(*b*) *Cannabis Indica:* Preceding excitement. Uncertain.

(*c*) *Hyoscin:* Especially in psychic exaltations and insanity.

6. *Mineral.*—Bromids (especially of potash): Supposed to act by simple depression of the activity of the brain-cells. No depression of medulla. Weak.

The drugs may also be grouped according to the form of insomnia in which they are especially indicated, as follows:

(*a*) In pain: *Morphin.* Large doses of *chloral* or *chloralose.*

(*b*) In *nervousness* or excitement or increased reflex irritability (tetanus, epilepsy): *Chloral Trional.*

(*c*) In delirium or worry: *Hyoscin, chloral, bromids.*

(*d*) In mild cases: *Alcohol, Urethane.*

When several of these indications exist, much good may be done by the combination of several hypnotics.

Contraindications:

Morphin and chloralose: Increased reflex irritability.

Chloral: Depression of medullary centers. Tendency to vascular, heart, kidney, lung, or gastric disease.

Sulfonal: Tendency to nephritis.

E. HYDROCARBON ANTISEPTICS (FORMALDEHYD GROUP.)

The hydrocarbons are antiseptic and irritant by coagulating protoplasm. This property appears in various degrees in the different members of the group: It is rather weak in the alcohols, ethers, and esters; it is rather stronger in chloroform and iodoform. (This last acts mainly by the liberation of iodin, and will be considered in another place.) The strongest antiseptic action is possessed by the aldehyds (acetaldehyd, paraldehyd, formaldehyd, acrolein).

The **formaldehyd** is the most important. It is one of the most powerful of antiseptics, and its usefulness is further enhanced by its ready volatilization and consequent penetration. Its irritant properties, on the other hand, limit its uses. The irritation can be greatly lessened by using the formaldehyd in the form of inactive and non-irritant preparations from which the active aldehyd is gradually liberated. The formaldehyd has the property of forming more or less stable **condensation products** with a large list of substances. such as proteids (*e. g.*, glutol); carbohydrates (dextroform, amyloform); phenols, urea; tannin (tannoform); ammonia (urotropin); and polymers (paraform). The urotropin can also form condensation products with proteids, etc. All these compounds may be utilized for the administration of formaldehyd. For disinfection outside of the body, the formaldehyd itself, in the form of its solutions or of the gas, deserves the preference. Glutol is especially useful as antiseptic powder; urotropin as urinary disinfectant; tannopin for intestinal antisepsis.

Formaldehyd, HCHO, is a colorless, irritant gas, discovered by von Hoffmann in 1868, and prepared by the oxidation of methyl alcohol. It is freely soluble in water, and is found on the market in the form of a 40% solution (*Formalin*).[1] The solutions tend to become inactive by the formation of the insoluble, polymeric paraform. This conversion is now prevented by chemic means.

Antiseptic Action.—Formaldehyd in solution inhibits the growth of bacteria when it is present in the proportion of 1 : 5,000 to 1 : 20,000, according to the species. It checks the growth in 1 : 30,000; stronger solution (½ to 2½%, according to the species and the time of exposure) kill all bacteria and spores. The gas is similarly antiseptic, especially when it is moist. Formaldehyd surpasses most other disinfectants in penetrating power, and does not injure metals or fabrics. It is employed, for *disinfection of rooms,* etc., as the gas, prepared by spraying the solution, by suspending sheets saturated in the solution, or best by the volatilization of paraform (see below); for *instruments and other articles,* it is used as ½ to 1½% solution; *feces* are deodorized immediately by a 1% solution; and rendered germ free in 10 minutes. *The propriety of its internal use may be doubted* on account of its irritant qualities, but it has been employed for the *disinfection of hands* (1%); as a *mouth-wash* and *gargle* (½%); in *skin diseases and hyperidrosis* (2.5%); for painting the throat in *diphtheria or tonsilitis* (2½ to 5%); and as *preservative* for milk and other foods and beverages (1 : 20,000 to 1 : 33,000). The *evaporation* of a small amount of the solution in the room has also been recommended in *tuberculosis.*

Action on Tissues and Body-Constituents.—The vapors of formaldehyd cause a very strong irritation of all *mucous membranes,* even when they are very dilute. The susceptibility to this irritation is diminished by *habituation.* Applied to the unbroken *skin,* it hardens the epidermis, renders it rough and whitish, and produces anesthesia. Repeated application of strong solutions leads to superficial *necrosis* of the skin and nails, and to persistent eczema (Galewsky, 1905). Its application to broken surfaces is very painful. Isolated tissues are promptly hardened. Formaldehyd is therefore used in *histologic technic* in the strengths of ½ to 10%. These effects are produced by the *coagulation of proteids.* The formaldehyd enters into actual combination with the serum or proteids, casein, gelatin, albumoses, etc. The combination may occur very slowly and the result is usually a precipitate or coagulum, which retains some COH_2 mechanically. This, as well as the combined COH_2, may be liberated in various ways, as by the action of bacteria, or by changing the reaction of the solution, etc. The *digestibility* of fibrin and the coagulability of casein are diminished. Formaldehyd also diminishes the activity of certain *ferments,* namely, papain, trypsin, ptyalin, and amylopsin; whilst pepsin, rennin, and malt diastase are but little altered.

Formaldehyd retards or *prevents the coagulation and spontaneous laking of shed blood,* when added in the proportion of 1 : 200 to 400. *Uric acid and urates* are dissolved, or their precipitation is prevented, by the formation of soluble compounds. *Urea,* on the other hand, forms an insoluble compound with formaldehyd.

Effects on the Body at Large.—The *inhalation* of formaldehyd vapors, even for a long time, produces but small effects, beyond the local actions, causing bronchitis and pneumonia. The *intravenous injection* of solutions in normal saline of a strength of 1 : 5,000 also causes no immediate effects, even in man. This measure has recently been recommended in *septicemia;* favorable results were produced, but these could be duplicated by the injection of the salt-solution alone. It may also be doubted whether these doses, although not immediately or conspicuously harmful, were really without deleterious action. The use of dilute solutions by mouth, in the form of *food-preservative,* is also without immediate harmful results, but is generally deemed to produce cumulative effects, by the irritant action, by the interference with ferments,[1] and perhaps also by the formic acid into which the aldehyd is oxidized. Even the local application may cause inflammatory changes in the liver and kidneys (Fischer, 1905). *Large doses,* injected into the blood, cause coagulation, with the production of methemoglobin and hematin. The symptoms are those of asphyxia. The *antidote* to the local action of formaldehyd is furnished by ammonia, well diluted, or by the ammonium salts. These also stop the antiseptic action.

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[1] In making solutions of a given strength, it is therefore necessary to take 2½ times as much of the commercial solution as would be required of absolute formaldehyd. The percentages given in this book refer always to *absolute* COH_2.

Fate: Small doses are destroyed completely in the body.

Liquor Formaldehydi (U. S. P.).—*Formalin,* Methanal. Not less than 37% of H.COH (an oxidation product of methyl alcohol). Colorless liquid of pungent odor and caustic taste. Misc. with water or alcohol. To prepare a solution of 1% absolute, add a tablespoon of the liquor to a liter or quart of water.

* **Paraform** (Trioxymethylen, Triformol).—$(H.COH)_3$.—This polymer occurs as a white, practically insoluble powder, often compressed into tablets. It sublimes slowly at 100° C. and melts at 171° C. Heated under proper conditions, it is decomposed into formaldehyd and is used for the *disinfection of rooms.* Two Gms. of paraform are required per cubic meter (35 cubic feet of space). Formaldehyd is also slowly liberated at body temperature: paraform is therefor useful as an *intestinal antiseptic* (0.05 to 0.1 Gm. every 2 hours, for children). It is more powerful than beta-naphthol, but its irritant action renders it objectionable. Larger doses (3 to 4 Gm.) are *cathartic,* small doses are rather constipating. It will not cause serious poisoning even in large doses.

* **Glutol.**—This is an odorless, non-irritant powder, formed by the combination of formaldehyd with gelatin. The COH_2 is liberated under the action of living tissues. The product is recommended as a *dusting-powder* for open wounds, on which it forms a firm, antiseptic scab.

Hexamethlenamina (U. S. P.).—(*Urotropin,* Hexamethylentetramin, Formin, Aminoform.)—$(CH_2)_6N_4$. Obtained by the action of ammonia on formaldehyd. Colorless, odorless crystals, of sweetish taste, with bitter after-taste. Sol. in 1.5 water, 10 alc. This compound is itself practically inactive, but if the urine is acid (not if it is alkaline) it is partly *changed into formaldehyd* in the course of its excretion. This excretion begins in a short time and may last several days. The urine therefor becomes antiseptic, and uric acid and urates are brought into solution. The drug is therefore used in *cystitis, gout, urate stone,* etc., and as a *diuretic.* The urate-solvent action is inferior to that of piperazin. The urinary antisepsis, on the other hand, is very valuable. The use of large or long-continued doses tends to nephritis, but this result is unusual.[2] The ordinary *dose* is 0.2 to 1 Gm. (3 to 15 grains), 2 or 3 times a day, in a tumbler of water, after meals (0.25 Gm. = 4 grs., U. S. P.) (Nicolaier, 1899).

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[1] Price (1904) has shown that the proportion which preserves milk, 1:10000, does not impede digestion *in vitro,* but the objections to the internal use of formaldehyd are not removed by this observation.

[2] Serious poisoning has sometimes been observed (see Medical News, New York, Aug. 29th, 1903).

* Not official.

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* *Citarin* (Anhydromethylencitrate of Sodium).— A white crystalline powder of agreeable, slightly acidulous taste; readily soluble in water, almost insoluble in alc. Liberates COH_2 in the blood. Recommended in gout and uric acid diathesis. *Dose:* 1 Gm. (15 grains).

* *Helmitol* (Urotropin-anhydromethylencitrate).— Fine colorless crystals, slightly soluble in water, decomposed by alkalies, and slowly by dilute acids, with liberation of COH_2. Used in the same conditions as urotropin. *Dose:* 1 Gm. (15 grains).

* *Tannopin* (Tannon) is a compound containing 87% tannin and 13% of urotropin. It is a brownish, tasteless powder, insoluble in water or dilute acids. In the intestine it is slowly decomposed, so that the antiseptic action of the urotropin and the astringent effect of the tannin is developed in the intestine, with a minimum of irritation. *Dose:* 0.5 to 1 Gm. (8 to 15 grains).

* *Tannoform* is an analogous compound of tannin and formaldehyd, with similar properties, but more irritant. It is used externally against excessive sweating, in the form of dusting-powder (with 1 to 3 parts of starch or talcum) or as a 10% ointment for eczema.

CHAPTER XX.

GASES.

General Remarks on the Action of Gases.— The respiration of oxygen is essential to life. A deficient supply of this gas leads to the phenomena of asphyxia. A number of gases (N, H, CH_4) act merely by excluding oxygen mechanically. This also forms an important element in the action of nitrous oxid, as ordinarily used. Carbon monoxid also acts by excluding oxygen, but it does so chemically. Other gases have specific, direct actions, especially on the central nervous system. Oxygen itself, when at a pressure of several atmospheres, is toxic. Carbonic acid and nitrous oxid produce their peculiar actions at lower pressures, but the air must contain considerable proportions. Sulphuretted and arseniuretted hydrogen are toxic in very small proportions. The gaseous acids (sulphurous, nitrous, etc.), alkalies (ammonia) and halogens (bromin and chlorid) act mainly as local irritants. Compressed air acts mechanically.

The effects of gases appear very *promptly* after beginning the inhalation, and disappear as rapidly when the animal is made to respire pure air. This is due to the large surface and large quantity of blood exposed to them in the lungs. As these factors are relatively greater in small mammals, these succumb and recover very much more rapidly than man, and may indeed be used as a test of the safety of a suspected air. Whilst the recovery from the direct effects of gases is rapid, indirect after-effects may be very persistent.

The quantitative effect of gases depends on their partial pressure in the air. At ordinary barometric pressure, this is equal to the volume-percentage of the gas. But it is important to remember that the effect of the normal percentage of oxygen at half an atmosphere pressure is the same as that of half the percentage at ordinary pressure; and conversely, that one per cent of a gas at three atmospheres produces the same effect as three per cent at one atmosphere.

The *symptoms* produced by most toxic gases resemble those of asphyxia, and this whether the effect is truly asphyxial (*i. e.*, produced by the absence of oxygen); or whether the gas has a specific toxicity. They are closely related to those of anesthetics.

A: OXYGEN.

The Inhalation of Pure Oxygen.— Oxygen constitutes about one-fifth (20.94%), by volume, of ordinary air. An increase of this proportion, and even *the inhalation of undiluted oxygen, produces no noticeable effect under ordinary conditions.* The rate of *oxidation* is not at all increased; indeed, the output of CO_2 is rather lessened. Evidently, the proportion of oxygen in air suffices for all ordinary needs (or, rather, it is greater than necessary); and additional oxygen acts merely as an indifferent gas — as so much nitrogen or hydrogen.

This statement needs some qualification. The reputed benefits from the inhalation of oxygen in *fatty degeneration and some other obscure diseases* (if the reports are reliable) would point to some effect on metabolism, perhaps too small to be detected by the usual methods of observation. The *out-door treatment of tuberculosis* may come under the same heading. **Oxygen under excessive pressures** (above 1.7 atmospheres) produces pneumonia; pressures above 3 or 4 atm. cause violent convulsions and ultimately death. These effects are not due to pressure as such, for they are not produced by compressed air until the partial pressure of oxygen reaches the above figures.

Caisson Disease occurs on the removal of an excessive pressure of air, *i. e.,* after coming out of the air-lock. On breathing compressed air, the nitrogen and oxygen are absorbed in the serum in proportion to their pressure. The oxygen is rapidly used in the tissues, but the nitrogen remains in solution. If the pressure is suddenly removed, the nitrogen is converted into gas, within the vessels, and produces embolism. The bubbles may be readily demonstrated. This may occur in various situations, producing a great variety of symptoms. These disappear promptly if the patient is again subjected to pressure, the gas going into solution. This is the proper method of treatment. If the decompression is made slowly, the gas is liberated so gradually that it can be eliminated, and no symptoms are produced.

Therapeutic Uses of Oxygen.— In striking contrast to the inefficiency of oxygen inhalations under ordinary conditions, is its very marked effect in asphyxia, *i. e.*, when the supply of oxygen is deficient, from any cause. The asphyxial symptoms, however alarming, are removed with marvelous promptness. It is especially effective in those forms of asphyxia, in which the access of oxygen to the blood is hindered, as by *vitiated air* (anesthesia, mines, wells, etc.); *by mechanical interference with respiration* (suffocation, drowning, croup, etc.); by *depressed respiration* (anesthesia, collapse); or by a diminished absorbing surface of the lung (*pneumonia*). In all these cases the blood is distinctly venous, *i. e.*, the hemoglobin is not saturated with oxygen; and the inhalation of the gas causes the saturation.

In *anemia* (whether from hemorrhage or any other cause, such as chlorosis or leucemia) asphyxial conditions result, not from deficient supply of oxygen, but from a deficiency of hemoglobin. The inhalation of oxygen, in these cases, does not increase the quantity of oxygen carried by the hemoglobin, but that carried in solution by the plasma. Whilst this is not very large in amount, it is sufficient to tide the patient over critical periods after hemorrhage, and to act as a general stimulant in other anemias.

Ordinary arterial blood contains about 18.5% of oxygen in chemic combination with hemoglobin; and 0.6% dissolved in the plasma — a total of 19.1%. Inhalation of undiluted oxygen increases the percentage in oxyhemoglobin only to 18.7%; the dissolved oxygen is increased in proportion to the partial pressure; *i. e.*, to 3%, giving a total of 21.7%, or an increase of 2.6%. This is not really as small as it appears; for it seems that the oxyhemoglobin does not yield all its oxygen to the tissues (for instance, after death by asphyxia the blood still contains considerable oxygen). Haldane considers that the increase of 2.6% really equals about 40% of the easily available oxygen of the blood.

The inhalation of oxygen is also useful, in an entirely analogous manner, in *advanced cardiac disease*, when the circulation is too slow to convey the required oxygen to the tissues. It acts also in the same way in *coal-gas poisoning*, where the carbon monoxid prevents the hemoglobin from combining with the oxygen. In this condition, as in anemia and cardiac disease, it is the increase of dissolved hemoglobin which produces the results; whilst in ordinary asphyxia, etc., it is mainly the oxyhemoglobin.

Administration.— Compressed oxygen is now obtainable in aluminum tanks. This is connected with a suitable mask, and the gas is administered according to the symptoms —

30 or 40 liters are generally needed. In emergency, the tube from the tank may be inserted directly into the mouth. The oxygen should be free from chlorin and ozone.

Ozone (O_3).— The presence of this gas in the air is often claimed as one of the attractions of health resorts, but it exists at best in extremely small amounts (*e. g.*, 0.015 to 15.8 milligrams in 100 liters of air). These could not have any effect of whatever kind.

Effects of Inhalation.— Ozone has not so far been obtained pure, since all the methods used for its manufacture also develop nitrous acid. The gas produced in this manner is quite a strong local irritant, causing inflammation of the mucous membranes, etc., and depresses the central nervous system. Smaller doses act rather as a narcotic (Sigmund, 1905), and later produce somnolence, convulsions, and finally death by edema of the lungs (Du Mont, 1891).

Ozone is distinctly antiseptic, but is so readily decomposed that its value is limited. Its use for the sterilization of water is said to be feasible, scientifically and commercially.

The Rôle of Oxygen.— Oxygen is an absolutely essential condition to the life of protoplasm. Organisms are indeed classified as aerobic and anaerobic — those which require *free* oxygen, and those which do not — but even anaerobic forms require oxygen in some shape. The oxygen as it exists in the air, or in most compounds, is not sufficiently active to effect the oxidations of the protoplasm; it must be in the form of active, atomic, "nascent," oxygen. This *liberation of active oxygen* is usually, if not always, accomplished by the action of *ferments*, "oxidases," which were first discovered in plants, but have since been demonstrated in most animal cells and tissues, especially in glands. They can be isolated by precipitating them from the extracts with alcohol. They may be recognized by the liberation of oxygen from H_2O_2 and by blueing guaiac. Their action is inhibited by heat, cyanids, and many other poisons. This same fermentative action is exerted by finely divided *metals*, especially in the "colloid" state, and these are inhibited by the same agencies.

The action of oxidases is *at once oxidizing and reducing; i. e.*, they reduce H_2O_2, and oxidize guaiac. In the tissues also powerful reductions and oxidations always go hand in hand. By appropriate color reactions it has been shown that the *cell-nucleus* is the principal seat of this reaction. A. P. Mathews (1905) favors the theory that cell respiration consists in hydration, rather than in oxidation, as in the rusting of iron; according to the formula $Fe + 2H_2O = Fe(OH)_2 + 2H$. The rôle of the atmospheric oxygen consisting in the removal of the liberated hydrogen, which would block the reaction in aerobic, but not in anaerobic organisms.

Oxidation is *favored by an alkaline reaction*, and retarded by acids. This is due to the fact that a large part of the oxygen supply is derived from the free OH ions, which exist in water by dissociation, which are increased by the addition of the OH ions of the alkali if this is added, but which are more firmly bound if acid is added.

The increase of available oxygen, up to certain limits, acts as a stimulus to all the functions of the protoplasm. In the case of free swimming forms, this gives rise to the phenomena of **chemotaxis:** If the organism is so placed that the concentration of oxygen is unequal at two different points, one will be more strongly stimulated than the other, resulting in movement until symmetrical structures are equally stimulated, *i. e.*, are exposed to equal concentration of the oxygen.

This "orientation" is also frequently accompanied by movement toward the greater concentration of oxygen (positive chemotaxis), or away from it (negative chemotaxis), according to the structures which are stimulated. There may also be a zone of optimum concentration, in which case the organism will swim in a limited belt at a definite distance from the oxygen. Plant-cells exhibit similar phenomena, which are called chemotropism (-tropism referring to inclination, -taxis to movement). Many other substances also produce chemotactic phenomena, the reaction varying with the special protoplasm.[1] Similar phenomena are produced by light (phototaxis); electricity (galvanotaxis); contact (stereotropism); gravity (geotropism); etc.

Lack of oxygen produces a series of well-defined functional, structural, and chemic changes in cells. The *functional changes* consist, in the case of nerve, in excitation, followed by loss of excitability; in muscle, there is first a loss of rhythmic activity, then of irritability. The *structural changes* consist in slight coagulation followed by softening, with increase of osmotic pressure and consequent swelling, absorption of water, vacuolization, and finally liquifaction. The *chemic changes* consist in the production of acid (generally sarcolactic), loss of synthetic power, but persistence of katalytic processes, *i. e.*, of breaking down of the protoplasm, with production of CO_2.

B. ASPHYXIA.

Asphyxia results from a deficiency of oxygen or an excess of carbon dioxid in the blood. The phenomena in both cases are almost, though not quite, identical. When asphyxia results from breathing in a confined space, both causative factors are intermingled.

The **symptoms** of asphyxia vary somewhat according to the rapidity with which it is produced. **When it occurs rapidly**, three typical stages may be distinguished: During the *first stage*, the respiration (particularly the inspirations) are increased. In the *second stage*, the respirations are irregular and convulsive, the inspirations being shallow and weak, the expirations powerful and prolonged. Consciousness is lost. The skin, and particularly the face, become cyanotic. The *third stage* is characterized by collapse and convulsions. The respiratory and vasomotor centers are depressed. The respiratory movements are shallow and infrequent. The convulsive, vagus and pupillo-dilator centers are stimulated. The extremities and the muscles of the face and neck twitch convulsively, there are gasping movements; the body of the animal is rigid and arched backward. Urine and feces are expelled. The pulse is very slow and soft, at first strong, then progressively weaker. The pupils are widely dilated until death. The heart continues to beat weakly for several minutes after the respiration has stopped. Artificial respiration during this interval will generally result in recovery. *Death* occurs within 6 or 8 minutes, if the trachea is tied.

The *autopsy* shows a very venous color of the blood. The veins of upper part of the body, and the right heart, are greatly distended

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[1] This simple theory does not seem to conform with some of the facts, particularly in infusoria (Jennings, 1905).

The effects on the *circulation* are shown in Fig. 47, page 151. Glycosuria is a common sequence.

If the asphyxia is produced slowly, the first symptoms are cyanosis and dyspnea on exertion. The individual becomes stupefied, but so gradually that he may not be aware of his condition. The stupor passes into unconsciousness and this into collapse. The motor symptoms may be entirely absent.

Asphyxia Through Lack of Oxygen.— This may result from a deficiency of oxygen in the air — by breathing rarefied air, or air diluted with indifferent gases (N, H, CH_4); by the presence of CO; by anemia; etc. Ordinary air contains about 21% of oxygen. It may be diluted until it contains only about 15% of oxygen (or may be rarified to the same degree), without producing any immediate effect.[1] At about 10% slight symptoms are noticeable, especially on exertion, but they are not alarming — dizziness, shortness of breath, deeper and more frequent respiration, quickened pulse, slight cyanosis. With 7%, these symptoms become serious, and stupor sets in. With a slightly lesser percentage, unconsciousness occurs. With 2 to 3%, death occurs within 45 seconds.

Exposure to slightly rarefied air, as on mountains, causes "**mountain sickness**" — nausea, headache, insomnia, etc. This generally disappears after a few days. A curious phenomenon is a prompt and persistent increase in the corpuscle and hemoglobin content of the blood (by 25 to 40%). This is due to a diminution of the plasma, the total quantity of hemoglobin being unaltered. The phenomena is not yet satisfactorily explained. Recent investigations indicate that the symptoms are due to deficient pressure of carbon dioxid in the blood.

Carbonic Oxid (*Carbon Monoxid*, CO).— **Occurrence.**— This gas has a toxicologic importance, for accidental or suicidal poisoning by its means are common. It constitutes 4 to 10% of ordinary *coal-gas*, and 30 to 40% of *water-gas* (which is consequently more dangerous). It is formed during *incomplete combustion* and is therefor present in the vapor of burning charcoal, after mine explosions, etc. It is the principal toxic ingredient of these gases. *Coal-gas*, however, is said by Vahlen (1903) to possess more than double the toxicity which would correspond to its CO. This is due to coal-tar products (which may be removed by passing the gas through oil). The disagreeable odor of gas is not due to the carbonic oxid (which is practically odorless), but to sulphur compounds. These are not toxic, but serve as a useful warning of the escape of gas. This odor can be detected in air containing 0.01 to 0.02% of gas; *i. e.*, much below the danger limit. They are removed by filtration through soil; so that underground breaks in gas-mains are especially dangerous.

Manner of Action.— Carbon monoxid combines with hemoglobin to form *carbonic-oxid hemoglobin*. The compound is very firm and is distinguished spectroscopically from hemoglobin by the fact that it is not reduced by ammonium sulphid. (See Fig. 79, page 378.) It has a cherry red color, which is quite different from that of oxyhemoglobin, especially when it is diluted. This forms the most delicate test for its presence.[2]

The affinity of hemoglobin for carbonic oxid is about three hundred times as great as that of oxygen; even *very small proportions* therefor prevent the complete oxygenation of blood, and produce *asphyxia*. It begins to be toxic when its quantity in the air reaches 0.05%; 0.16% is dangerous; 0.4% is generally fatal. The symptoms do not differ from those of other forms of asphyxia, except by the absence of the cyanosis; the skin being pink or pale, and the lips bright red (*i. e.*, the color of CO-hemoglobin). This is of diagnostic importance. The effects are insidious, the person becoming unconscious often with no premonitory symptoms. Dizziness and hyperpnea occur when about 20% of the hemoglobin is saturated; unconsciousness with 50%; death with 60 to 85% of saturation.

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[1] A candle will be extinguished when the oxygen has fallen to about 17.5%, and is therefore a test for the safety of the air, as far as oxygen is concerned.

[2] Exercise 21.

Carbonic oxid acts only by displacing oxygen and has no direct action of any kind; for if an animal is made to breath oxygen under two atmospheres pressure (which renders it independent of the hemoglobin) the addition of carbonic oxid in any amount produces no symptoms.

Treatment.— In the presence of a large excess of oxygen, the carbonic oxid hemoglobin is again decomposed, and the CO eliminated (not burned). The treatment therefor consists in artificial respiration, or still better, the forced inhalation of oxygen. The *patient should not be exposed to cold.* Recovery is rather more slow than with most gases; but the acute effects have generally disappeared within three hours. Very persistent *after-effects* are, however, quite common. These consist of headache, nausea, pneumonia (often fatal), paralysis, chorea, and loss of memory. The latter is especially common. The nervous effects have been referred to a serous leptomeningitis (Zieler, 1897).

Carbon Dioxid (*Carbonic Acid*, CO_2).— The effects of this gas are almost indistinguishable from those of lack of oxygen. They are not due to the latter, for they occur even when oxygen is present in excess. They are produced by the direct action of the dissolved carbonic acid on the tissues, especially on the central nervous system.

As an instance of its direct toxicity, it may be mentioned that the perfusion of the coronary vessels of a mammalian heart with CO_2 causes prompt fibrillation and arrest, whereas the heart continues to beat for a considerable time if the perfusion is made with oxygen, or even hydrogen (Magnus, 1902).

The presence of carbonic acid in the air is a coöperative factor in many forms of asphyxia; its importance, however, is generally exaggerated. Pure air contains 0.03% of CO_2; in city streets it rarely rises above 0.04, or at most 0.15%. In badly ventilated rooms it may reach 0.3%; whilst 3% is the smallest proportion which produces any noticeable symptom, and even 10% does not cause unconsciousness; 25% may be fatal after several hours. Neither the presence of CO_2, nor the absence of oxygen explains the harmful effect of sojourn in ill-ventilated rooms; nor does the expired air contain any poisonous ingredients. It is supposed that the acute discomfort and the suffocating sensation experienced in these places is largely psychic, being produced by the heat, odors, noise, etc. Whether this will also account for the severely detrimental effect on health and resistance, the increased tendency to tuberculosis, etc., which are associated with habitually deficient ventilation, is an open question.

It may be remarked that the continued or repeated exposure to gases — particularly those acting upon the blood, and indeed to any poison which alters the blood, such as acetanilid — never causes tolerance, but usually increases the susceptibility.

C. NITROUS OXID (LAUGHING GAS, N_2O).

This gas has been mentioned under the general anesthetics, which it greatly resembles in its actions.

The *symptoms* are at first those of *excitement*, usually of a pleasant variety (laughter, etc.). Then follow *loss of sensibility* to pain, and incoördination of movements. This is as far as the action goes when the gas has been mixed with 20% of oxygen. If *pure gas* is used, or the mixture is used under pressure, these symptoms pass into those of **asphyxia**: loss of consciousness, heightened reflexes passing into convulsions, and later paralyses from the effect on the spinal cord. The effects upon the **medulla** lead, in the stimulant stage, to a *quickening of the respiration* and *stimulation of the vasomotor center,* with consequent high blood pressure. This latter is of some importance, since it is said to have given rise to *apoplexy* in persons predisposed to this. Later, both the respiratory and vasomotor centers are paralyzed as well as the heart muscle.

These effects are plainly referable, in large part, to the exclusion of oxygen; for although nitrous oxid supports ordinary combustion, it cannot take the place of oxygen in life processes. This asphyxia may be prevented, and the specific action of nitrous oxid studied, by using a mixture of four parts of gas and one part of oxygen, under a pressure of one and one-fourth atmospheres. Complete anesthesia without asphyxia may be kept up in this manner for several days. Evidently the nitrous oxid has a direct action on the central nervous system; first stimulating the psychic areas, then depressing these to insensibility. The motor reflexes are also abolished. The medullary centers are not affected, and the circulation remains unchanged, in the absence of asphyxia. Nitrous oxid also has no action on other tissues. It does not combine with hemoglobin.

The mechanism of its central action is probably the same as with the hydrocarbon narcotics — viz., a physical change in the lipoids. On account of its feeble chemic affinities, the gas is practically free from side-actions, and herein lies its chief value.

Anesthesia by Undiluted Gas.— For very short operations (as in dentistry) the gas is inhaled through a tightly fitting mask, with the exclusion of air, until the face becomes cyanotic, the breathing stertorous, the pupils enlarged, and the patient unconscious. This occurs in 63 to 80 seconds. The gas is then removed and the operation performed at once, the anesthesia lasting only 22 to 30 seconds. The time from beginning the inhalation to complete recovery is only 100 to 120 seconds. There is very little nausea and no other after-effect. The anesthesia is due to the combined action of the gas and of asphyxia; but mainly to the latter. It cannot therefor be prolonged. For short operations, it is the least dangerous of anesthetics: Only 17 deaths have been reported, making a fatality of about 1 : 5,250,000. In case of accident, artificial respiration, or preferably oxygen, should be applied.

Anesthesia by Nitrous Oxid Diluted with Oxygen.— The anesthesia may be prolonged indefinitely by mixing the nitrous oxid with twenty per cent of oxygen, and using it under an excess pressure of one-fourth atmosphere. Even lesser proportions of oxygen permit a more or less lasting anesthesia. This principle has been utilized in practice. A special apparatus is required, allowing the mixture of the two gases in any proportion. This is connected with a close-fitting mask. It is advisable to warm the gas mixture before it is inhaled.

To hasten the anesthesia, the administration is begun with a mixture containing 2% of oxygen. This is gradually increased to 10%.

The induction of anesthesia is very rapid, perhaps 12 to 15 minutes. The patients recover consciousness at once. The nausea is very slight, and with this method of administration there is no marked asphyxia — at most a slight cyanosis. The anesthesia is most readily induced in children or old people, is much more difficult in hysterics and alcoholics, sometimes failing entirely. The gas has, however, some disadvantages: Its administration requires skill and constant watching, since either recovery or asphyxia occur very rapidly. The muscular relaxation is not nearly as complete as with ether.

This method of anesthesia has proved especially valuable as *a preliminary to other anesthesia* (see page 437). Its principal drawback is the expense and inconvenience of the apparatus and the expense of the gases.

(By great skill and care in regulating the distance of the mask from the face, a prolonged anesthesia may be kept up with nitrous oxid, without oxygen).

D. OTHER TOXIC GASES.

Nitric peroxid (NO_2) and **Sulphurous Acid** (SO_2) are very toxic by local irritation, producing bronchitis and pneumonia. SO_2 produces extreme discomfort in proportions as small as 0.001% (0.1% being fatal). NO_2, on the other hand, produces but very slight acute effects, followed by severe and often fatal bronchitis. It is therefor especially dangerous. It is produced in large amount in the combustion (not in the explosion) of nitroglycerin and gun-cotton.

Hydrogen Sulphid (H_2S) is extremely toxic. Its effects are partly local, partly central. The former are irritant, due to its acid character; the latter resemble asphyxia. It is formed in putrefaction, particularly of sewerage; 0.02% produces symptoms, particularly irritation of the conjunctiva and bronchial mucosa; 0.05% produces asphyxial symptoms: hyperpnea, nausea, giddiness, headache, etc; 0.07% produces death after about an hour; 0.2% is fatal to dogs in 1½ minutes. The after-effects resemble those of carbon monoxid. Edema of the lungs and pneumonia are common sequels.

Hydrogen sulphid does not act by combining with hemoglobin, under ordinary conditions, but acts directly on the tissues. It is readily detected in air by its odor and by blackening lead or silver-paper. In case of death, it may be recognized by the blackening of a silver coin laid on the skin.

Arseniuretted Hydrogen (AsH_3).— Its action is different from that of arsenic. It produces a destruction of blood-corpusles (also in vitro) and consequently anemia, icterus, and hemoglobinuria. For the rest, it causes nephritis and general asphyxial symptoms. It is impossible to say at present whether these asphyxial symptoms are due to the direct action of the drug on the respiratory center, or to the diminution of the blood-corpuscles.

CHAPTER XXI.

(A) CAMPHOR GROUP.

I. MEMBERS.

Camphor and substances chemically allied to it — *i. e.*, camphoric acid, monobromated camphor, Borneo camphor, menthol, thymol, musk, etc.

Camphor is a stereoptene — *i. e.*, a solid body deposited from a volatile oil. Chemically it belongs to the terpenes, having for type turpentine, $C_{10}H_{16}$. This group may be split up, so that there are hemi-terpenes, C_5H_8, sesqui-terpenes, $C_{15}H_{24}$, etc.

The bodies belonging to this group have the following composition:

$C_{10}H_{16}$ = Turpentine.

$$C_{10}H_{16}O = \text{Camphor} \left\{ \begin{array}{ll} C_{10}H_{16}O_4 & = \text{Camphoric Acid.} \\ C_{10}H_{15}BrO & = \text{Monobromated Camphor.} \end{array} \right.$$

$C_{10}H_{18}O$ = Borneo Camphor.

$C_{10}H_{20}O$ = Menthol.

The camphor group is related in composition and actions to the volatile oils, and more remotely to carbolic acid. The principal difference from the latter consists in the greater predominance of the stimulation in the case of camphor. This, as with picrotoxin, is exerted mainly on the medulla.

II. SUMMARY OF ACTIONS.

1. Stimulation of the central nervous system, followed by paralysis in large doses. The main action in mammals is on the vasomotor center.
2. Stimulation of the cardiac muscle.
3. Locally, stimulation and paralysis of the sensory nerve endings; also stimulation of the nerves conveying the sensation of cold in the case of menthol.
4. Peripheral depression of the tonus of blood vessels.
5. Mildly antiseptic, after the manner of essential oils.
6. A curare action on striped muscle.

III. DETAILS OF ACTION.

1. Central Nervous System.[1] — **(a) Brain:** The stimulant symptoms begin in man with *impulsive movements*, confusion, *delirium;* then follows *unconsciousness* with *epileptiform convulsions.* The latter have been attributed to stimulation of the medulla, but some experiments seem to show that they are, at least partly, located in the brain. The lower animals give expression to this excitement by increased motion.

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[1] Exercise 39.

(b) Stimulation of the medulla is shown in man first by *vertigo;* later all the medullary centers are stimulated; the *respiration* is increased in volume and rate. The *blood pressure* rises; the *face and skin are flushed,* due to stimulation of the vasodilator center. *Large doses paralyze* the medulla and cause *death by collapse.*

The (c) **spinal cord** also shows some *stimulation, and finally paralysis,* but this *does not come on until late,* and is not important *in mammals.*

(d) In **frogs,** on the other hand, the action on the spinal cord is *very pronounced,* and consists in a *paralysis.* This entirely obscures any action which the drug may have higher up in the nervous system in these animals. It appears that the path for reflex impulses is blocked before that for impulses coming from the higher brain.

2. **Action on the Circulation.**— The action of camphor on the circulation is quite complicated, since it acts to a variable degree on the vasomotor center (increased excitability); on the arterial muscle (loss of tone, by peripheral action); and on the cardiac muscle (stimulation). The *cardiac stimulation* is not seen with small and medium doses in *mammals.* Larger doses may cause recovery of a fibrillating excised heart, and prevent delirium cordis from electric stimulation (Seligmann, 1905). They may also revive the heart when poisoned by potassium. Still larger doses produce direct cardiac depression. Some investigators have observed a periodic stimulation of the *vasomotor center,* a rhythmic rise of the blood pressure; but more recently this has been denied (Seligmann). The blood-pressure usually falls, through direct depression of the arterial muscle.

The *frog's heart* is slowed and strengthened. This stimulation is seen particularly when the heart has been depressed by any poison, so that it must be mainly muscular.

3. The **local action** is similar to that of the essential oils, or of very dilute carbolic acid, producing some *irritation and then anesthesia.* This determines its use for local application in liniments. **Menthol** shows a peculiar stimulation of the nerves conveying the sense of *cold.* The skin *feels* cooled after the application of the substance, although there is no fall in the temperature, the vessels in fact being dilated. The irritability of the endings for the sensation of heat is also increased.

The *irritant action* of small doses of camphor *on the digestive canal* is used *against dyspepsia.* Large doses produce *vomiting.*

4. Applied directly to frog's skeletal muscle, it produces a **curare-like action.** This is not seen in mammals.

5. Camphor has a slight **antiseptic action** which determines its use in mouth-*washes* and *gargles;* and it also forms a quite efficient *intestinal* antiseptic, the amount of combined sulphates in the urine being lessened by it.

IV. ABSORPTION AND FATE.

On account of its volatility camphor is absorbed quite readily, although it is insoluble. However, the absorption presents very great variations, which make the action extremely uncertain, and greatly interfere with its usefulness in therapeutics. The members of this group are converted in the body into hydroxyls, unless they already contain this radicle. (Fromm and Hildebrandt, 1901.)

The actions of the

V. OTHER MEMBERS OF THE SERIES.

are so similar to those of camphor that the preceding description applies to them also. They have no advantage over camphor in therapeutics. *Musk* is supposed to act in the same way, but almost nothing is known about this substance. *Camphoric acid* has a peculiar action on diaphoresis (see Index).

VI. THERAPEUTICS.

1. Camphor has considerable reputation as a circulatory and respiratory stimulant in conditions of *collapse*, syncope, adynamic fevers, cardiac failure, etc. For this purpose it should be administered hypodermically, ½ c. c. of the camphorated oil being injected every fifteen minutes for four doses. The effect has been explained partly by reflex stimulation from the pain of the injection, partly by the direct action of the camphor on the nerve-centers and heart; animal experiments are, however, negative. The clinical success is also inconstant. This has been referred to the *uncertain absorption*. Since these doses of camphor can do no harm, they are worthy of trial.

On the other hand, camphor has been used as a *nervous depressant* in epilepsy, chorea, and convulsions, and as an *anaphrodisiac*, and so on. This rests on no rational basis.

It has also been employed against *hysteria*, but considering the uncertain course of this disease, it is impossible to say whether camphor is of any benefit.

2. **The dilation of the cutaneous vessels** makes camphor useful as a **diaphoretic** and in *colds*.

Like the other terpenes, Camphor has found some employment in *tuberculosis*. The least objectionable method would seem to be give it as emulsion per rectum, about

1 Gm. per day. It has also been used subcutaneously, 0.01 Gm. dissolved in oil, being injected daily. Most observers report it as unsatisfactory.

3. Camphor is used for its **local action** on the skin as a *counterirritant,* and for its *local anesthetic* effects. For the latter, *menthol* in the form of menthol pencils is especially useful. It is rubbed on the forehead in headache, or inhaled. Camphor itself is employed in the form of spirits of camphor or oil of camphor, often as an ingredient of liniments.

4. Its local effects upon the gastric and intestinal canal have caused its employment in **dyspepsia** and as a *carminative* and *intestinal antiseptic.* For this purpose, 0.3 Gm. is taken three times a day. Like the essential oils, it forms a frequent addition to *gargles and mouth-washes.*

VII. MATERIA MEDICA.

Camphora (U. S. P., B. P.).— *Camphor.*— $C_9H_{16}CO$.— A stereoptene obtained from *Cinnamomum Camphora,* Laurineæ; China and Japan.

The wood is distilled with water and the solid Camphor separates from the distillate. It is further purified by sublimation. Very sparingly soluble in water, freely in alcohol, etc., and in fixed and volatile oils. *Dose:* 0.05 to 0.3 Gm. (1 to 5 grains) (0.125 Gm. = 2 grs., U. S. P.).

Preparations:

Aqua Camphoræ (U. S. P., B. P.).— A saturated aqueous solution; very little therapeutic action. *Dose:* 8 c. c. = 2 ʒ (U. S. P.).

Spiritus Camphoræ (U. S. P., B. P.).— A 10% solution in alcohol; not miscible with water. The best form for internal administration. *Dose:* 1 to 4 c. c. (15 to 60 ♏) (1 c. c. = 15 ♏. U. S. P.).

Linimentum Camphoræ (U. S. P., B. P.).— *Camphorated Oil.*— A 20% solution in Cottonseed Oil. Best form for external use.

Linimentum Camphoræ Ammoniatum (B. P.).— Contains camphor, ammonia, alcohol, and oil of lavender.

Ceratum Camphoræ (U. S. P.).— 10%.

Tinctura Camphoræ Comp.— (B. P.) (Paregoric).— See Index.

* *Camphor-Chloral* (N. F.).— Equal parts. Used externally.

Camphor is also contained in the following pharmacopœial preparations: Linimentum Belladonnæ; Linim. Sinapis Comp.; Tinct. Opii Camph.; Pulvis Morphinæ Comp.

* *Borneo* (*Sumatra*) *Camphor.*— $C_{10}H_{18}O$.— From *Dryobalanops Camphora,* Dipterocarpeæ.

Camphora Monobromata (U. S. P.).— $C_9H_{15}Br.CO$.— Made by heating Bromin and Camphor. Insoluble in water, soluble in alcohol. *Dose:* 0.12 to 0.6 Gm. (2 to 10 grains) (0.125 Gm. = 2 grains, U. S. P.).

* *Oxycamphor* (camphor with H replaced by OH) has been recommended as respiratory sedative in cough. It is a crystalline powder, of a peculiar odor and a bitter, pungent taste. The aqueous solution

decomposes, and it is marketed as a 50% alcoholic solution, of which the *dose* is 1 c. c. (20 drops).

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* Not official.

Study Materia Medica Lesson 35.

Acidum Camphoricum (U. S. P.).—$C_8H_{14}(COOH)_2$. Obtained by the oxidation of camphor. Colorless crystals. Sol. in 125 water, readily in alcohol and fatty oils. *Dose:* 0.6 to 2. Gm. (10 to 30 grs.) (1 Gm. = 15 grs., U. S. P.). Said to be specific in night-sweats of phthisis.[1] Two Gm. are given two hours before the expected sweat. Externally: As a mild antiseptic gargle, wash, and injection in the manner of Camphor, over which it has the advantage that it can be dissolved in any proportion by adding 10% of alcohol for each % of camphoric acid. It is usually employed in strengths of from 0.5% to 6%.

* *Agaricin,* from *Boletus Laricis* (*Dose:* 0.005 to 0.03 Gm.), is also used in these night-sweats. Large doses paralyze the heart and respiration.

Menthol (U. S. P., B. P.).—$C_6H_9(CH_3)(OH)(C_3H_7)$ 1 : 3 : 4. Stearoptene derived from the volatile oil of various species of Mentha. Slightly soluble in water, freely in alcohol. *Dose:* 0.03 to 0.12 Gm. (½ to 2 grains) (0.065 Gm. = 1 gr., U. S. P.).

Emplastrum Menthol (B. P.).—25%.

(B) HYDROCYANIC ACID GROUP.

I. OCCURRENCE.

Hydrocyanic acid exists as amygdalin in many plants. This amygdalin, when pure, is almost entirely harmless, except as it is decomposed in the body. But in most plants it coexists with the ferment emulsin, by which it is split up in the presence of water into hydrocyanic acid, glucose, and benzaldehyd:

$$C_{20}H_{27}NO_{11} + 2H_2O = 2C_6H_{12}O_6 + HCN + C_6H_5.CHO.$$

One gram of cherry kernels yields 1.7 mg. hydrocyanic acid; one gram bitter almond pulp yields 2.5 mg. hydrocyanic acid.

The most important cyanogen (CN) compounds are the acid (prussic acid, official as the dilute, 2% solution) and cyanid of potassium. Mercury cyanid has mainly a mercury action. The cyanid action is also shared by the organic esters (*nitrils*); these differ from potassium cyanid only in the rapidity with which the cyanogen is liberated. Ferri and ferro-cyanids (red and yellow prussiate of potash), sulfocyanids, and nitroprussids do not show the cyanogen actions, unless decomposed. The ferro, ferri, and sulfo-cyanids are fairly staple, and consequently have little effect. *Nitroprussids,* however, liberate CN readily and *agree with cyanids,* except that they are less convulsive.

II. SUMMARY OF ACTIONS.

1. Toxicity to all forms of protoplasm and to ferments.
2. Stimulation and paralysis of the central nervous system; the effects being analogous to those of asphyxia. They are produced by interference with the oxygen consumption by the tissues.
3. Peripheral vasodilatation, at least in the kidney.
4. With methemoglobin, it forms cyanhemoglobin, giving a peculiar spectrum.

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[1] Camphoric acid is only effectual in checking the sweats of phthisis, so that it must act differently from atropia.

* Not official.

III. DETAILS OF ACTION.

Hydrocyanic acid interferes with the action of *all ferments*. It even hinders the inorganic "ferments" (spongy platinum, etc.).[1] It is a *violent protoplasmic poison*, presumably through its restraint of the fermentations which play a most important rôle in life processes. All forms of life, all tissues and organs, are affected. Infusoria are killed in a concentration of 0.1%. The growth of yeast and of higher plants, the germination of seeds, the contractility of animal cells, the conductivity of nerves, etc., are inhibited. If the action is sufficiently continued, all vitality is destroyed; but if the cyanid is promptly removed, complete recovery occurs. Direct application of hydrocyanic acid causes *local anesthesia*.

In *excised kidneys* perfused with saline solution, the addition of hydrocyanid acid causes a very marked dilation of the renal vessels. The effect is apparently due to a paralysis of the arterial muscle. It disappears promptly on removing the cyanid (Sollmann, 1905).

Effect on Higher Animals.— When given in doses small enough to permit of watching its action, this is seen to consist in a *fleeting stimulation of certain parts of the* **central nervous system,** *followed by depression* and paralysis. The action *begins in the medulla.* The vomiting, respiratory, vagus, pupil-dilator, and vasomotor centers are all stimulated. Then comes *unconsciousness,* and after this *convulsions.* In man these are probably mainly medullary in origin. Then follows paralysis of the whole central nervous system. Involuntary evacuations of feces, urine, and semen are frequent.

The *respiration* is at first greatly increased, especially in depth; it then becomes slow, shallow, and irregular (Cheyne-Stokes type (Fig. 52, page 185). It stops considerably before the heart, paralysis of the respiratory center being the immediate *cause of death.* The effect on the circulation is entirely analogous to that of asphyxia (see Fig. 47, page 151). As in the latter, the heart may again execute a few movements after it has stopped for a time (*h* in the figure); but these do not suffice to maintain the circulation.

Applied directly to the *frog's heart,* cyanids cause a standstill, which is not removed by atropin; however, the heart responds strongly to electric or mechanic stimulation. The paralysis evidently involves the automatic property of the cardiac muscle. There is no evidence of this action in the blood-pressure tracings from mammals.

IV. EXPLANATION OF THE ACTION.

The phenomena of the action of hydrocyanic acid on the central nervous system — the stimulation of the medullary centers, the convulsions, the vascular paralysis, etc.— bear a close resemblance to those of asphyxia; and it can be easily shown that oxidation is enormously diminished. There is, however, one very marked difference from ordinary asphyxia, for the blood remains of a bright arterial color,[1] indeed, the oxygen content of the venous blood in cyanid poisoning approaches that of ordinary arterial blood. It is evident that the oxygen supply to the tissues is not lessened. The cause of the asphyxia, of the lessened oxidation, must lie in the protoplasm of the tissues. This undergoes what might be termed "*internal asphyxia,*" in sight of abundant oxygen (Geppert, 1889).

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[1] The analogous effect on organic and inorganic ferments does not necessarily imply any analogy in the mechanism of the actions. That on metals is probably produced by a minute film of cyanid.

It may be assumed that the cyanid interferes with the fermentative processes by which the utilization of oxygen is accomplished; just as it hinders oxidative ferments without the body. Its effects on lower organisms are also precisely the same as those of deprivation of oxygen.[2]

Hydrocyanic acid unites with ***hemoglobin,*** but this combination is of a different nature from that with carbonic oxid, and has no influence upon the readiness with which oxygen is given off. When added to methemoglobin, it causes the formation of cyan-hemoglobin, which differs from ordinary hemoglobin in its bright red color and in a peculiar band (Fig. 79, page 378). This compound is responsible for the bright red ecchymotic spots seen after hydrocyanic poisoning. Methemoglobin can be used as a test for hydrocyanic acid.

Fate.— Hydrocyanic acid is very unstable; it changes very readily, even by mere exposure to light and air; and it undergoes still quicker decomposition in the body. Part of it combines with sulphur-containing molecules to form sulphocyanids. The fate of the remainder is unknown.

Sulphocyanid is found in the human parotid **saliva,** whilst it is absent in that of all other animals. The nervous connection of the gland must be intact, for it is absent in middle-ear disease, for instance. Its significance is not understood, but it does not result from bacterial decomposition as was formerly supposed. Its amount can be increased by taking HCN — even that existing in tobacco smoke causing an increase.

V. TOXICOLOGY.

Hydrocyanic acid is not very much used in criminal poisoning (0.5% of the recorded cases), because its quick action would soon lead to the detection of the crime. On the other hand, it or the cyanids form very favorite methods with suicides. On account of the technical uses of potassium cyanid (in photography, electroplating, cleaning of metals, etc.), it can generally be obtained with little trouble. Some cases are also reported of accidental poisoning by the gaseous acid.

This pure hydrocyanic acid, which is never seen outside of chemic laboratories, is extremely volatile and very toxic. The famous chemist Scheele, who discovered hydrocyanic acid, was killed by the vapors set free in the breaking of a flask of this fluid.

The **strength** of the official (dilute) acid should be **2%**; but many samples are much weaker, on account of decomposition. Potassium cyanid is still more variable. The pharmacopœia requires a strength of 90%; but the commercial article sometimes contains only 30 or 40%. This accounts in part for the variability in the appearance and severity of the symptoms. Another variable factor is the *rate of absorption,* according to whether the stomach is full or empty. In the latter case, there is a much better chance of saving the patient. However, the absorption is always very rapid; it occurs even to some extent from the intact skin. Application to raw surfaces or to cuts has given rise to poisoning. Inhalation of the vapors has proven fatal.

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[1] Exercise 72, No. 5.

[2] In certain fish-ova, cyanids also suspend the autolytic processes accompanying death, so that the cells remain in a condition between life and death for several days (Sollmann, 1906).

The **fatal dose** of absolute HCN is about 0.05 Gm. ('1 grain); that of KCN is 0.2 to 0.3 Gm. (3 to 5 grains); that of dilute hydrocyanic acid, would be about 2.5 Gm., 50 or 60 Bitter almond seeds, would be fatal. Correspondingly larger doses are needed if the drugs are impure or decomposed. The impression prevails quite widely that prussic acid is one of the most powerful poisons. This reputation is justified by its *extremely rapid action,* rather than by its toxic dose.

In the so-called **apoplectic form**; *i. e.,* when very large doses are taken, the patient may fall unconscious, often with a loud cry, within ten seconds,[1] and die within two to five minutes, after some convulsions. Ordinarily, the course is rather more prolonged; several minutes may elapse after taking the poison before any effect is noticed; death occurs between 15 minutes to an hour.

The **symptoms** consist in vertigo, mental dimness, headache, palpitation; then comes dyspnea, which may become very violent from stimulation of the respiratory center; the patient then becomes totally unconscious and shows very violent convulsions. During this stage the heart may be greatly quickened. The respiration becomes first difficult and then ceases. The heart at this time is very much weakened, but still continues to beat for a short time and then stops.

The prompt **diagnosis** of cyanid poisoning is very important in view of the treatment. The odor is very characteristic. (The student should familiarize himself with the appearance and odor of potassium cyanid.) The very rapid onset of the symptoms is also characteristic.

At the **autopsy,** the *odor* is also noticeable on opening the body. There are no peculiar *lesions,* except with potassium cyanid, which acts as an alkaline caustic. The *blood* is generally liquid, and remains so after removal from the body (by interference with the fibrin ferment). Its color is stated to be very dark — but this is not true of all cases: it may be of a very bright arterial color. Bright red

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[1] This is the shortest time reported — a fact which may be of some medicolegal importance if the question arises what acts the patient could have performed after taking the poison.

ecchymotic spots, due to cyan-hemoglobin, occur during putrefaction. The final *proof* of cyanid poisoning rests on chemic tests (see Index). The poison disappears within two weeks during putrefaction; but remains for a long time if the latter is prevented and if there is no evaporation.

Treatment.— This consists in the prompt *evacuation* of the stomach with lavage. The *chemic antidotes* should be added.

These consist of hydrogen peroxid ($2HCN + H_2O_2 = (CO)_2(NH_2)_2$, oxamid); potassium permanganate (0.25 to 0.5%); arsenic antidote; cobaltous nitrate (0.5%); or sodium hyposulphite (1%). (The last acts probably by forming sulphocyanid; the metals form ferricyanid and cobaltocyanid.)

These measures are quite successful in animals, if they are administered conjointly with the cyanid. In man, they have yielded less promising results, since too much time elapses. The peroxid and hyposulphite should be tried, however. The latter should also be injected intravenously (0.5 to 1%, added to 0.6% NaCl) or hypodermically (3%), using 100 to 500 c.c.

It is also justifiable to bleed the patient profusely, replacing the blood by saline solution.

The *symptomatic treatment* consists essentially in supporting the respiration. Brisk artificial respiration should be begun at once and maintained as long as the heart beats. This acts mainly by aiding the elimination of the poison through the lungs. Counterirritation, and general stimulants (caffein and atropin) may also be used. If the patient survives an hour, the danger is practically passed. There may be some sequels — headache, tremors, etc. The *mortality* is very high — 95%.

The repeated administration of subletal doses of cyanids leads to chronic cachexia, without altering the susceptibility to the poison (Schlegel, 1892).

VI. THERAPEUTICS.

There seems to be no rational basis for the therapeutic use of the cyanids, except as flavors.

The *local anodyne action* is used against *itching of the skin* and pruritus, against *cough*, and against *vomiting*. If given internally, it must be in *small doses frequently repeated*, on account of the rapid decomposition. Hydrocyanic acid has also been given for other purposes, especially in *phthisis*.

VII. MATERIA MEDICA.

Acidum Hydrocyanicum Dilutum (U. S. P., B. P.).—(*Prussic* Acid.)— Should contain 2% of HCN. Made by decomposing Pot. Ferrocyanid with H_2SO_4, and distilling, or extemporaneously by precipitating silver cyanid with hydrochloric acid. Colorless liquid of characteristic odor. Very unstable; a black precipitate develops in time, and the strength decreases rapidly. Incompatible with metals. *Dose:* 0.06 to 0.2 c. c. (1 to 3 minims) (0.1 c. c. = 1½ ♏., U. S. P.).

Potassii Cyanidum (U. S. P.).— KCN. Prepared by fusing Pot. Ferrocyanid with Pot. Carbonate and crystallizing. The official contains at least 95% of KCN, but the commercial articles are often very much weaker. Sol. in 2 parts of water, sparingly in alcohol. Decomposed by boiling water. *Dose:* 3 to 15 mg. (1/20 to ¼ grain) (10 mg. = ⅕ gr., U. S. P.).

Drugs and Galenic Preparations containing HCN:

Prunus Virginiana (U. S. P.) [Prunus Virginianæ Cortex, B. P.].— *Wild Cherry.*—The bark of *Prunus serotina;* Rosaceæ; North America. Tannin; Amygdalin; Bitter glucosid.

Tinctura Pruni Virginianæ (B. P.). —10 c. c. *Dose:* 2 to 4 c. c. (½ to 1 drachm).

Fluidextractum Pruni Virginianæ (U. S. P.).— *Dose:* 2 to 4 c. c. (½ to 1 drachm) (2 c. c. = 30♏., U. S. P.).

Infusum Pruni Virg. (U. S. P.).— 4 : 100. *Dose:* 60 c. c. (2 ozs.).

Syrupus Pruni Virg. (U. S. P., B. P.).— 15%. *Dose:* 4 c. c. = 1 ʒ (U. S. P.).

Amygdala Amara (U. S. P., B. P.).— *Bitter Almond.*— The seed of *Prunus Amygdalus,* var. Amara, Rosaceæ; Mediterranean. Contains Amygdalin, fixed and volatile oil, etc.

Aqua Amygdalæ Amaræ (U. S. P.).— *Dose:* 4 c. c. = 1 ʒ (U. S. P.).

Oleum Amygdalæ Amaræ (U. S. P.).— The volatile oil. *Dose:* 0.03 c. c. = ½ ♏. (U. S. P.).

Spiritus Amygdalæ Amaræ (U. S. P.).—A 1% alcoholic solution of the oil. *Dose:* 0.5 c. c. = 8 ♏. (U. S. P.).

Laurocerasi Folia (B. P.).— Leaves of *Prunus Laurocerasus,* Rosaceæ (Cherry-Laurel).

Aqua Laurocerasi (B. P.).— Contains 0.1% HCN. *Dose:* 2 to 4 c. c. (½ to 1 drachm).

(C) GROUP OF NITRITES.

This group comprises the inorganic nitrates ($NaNO_2$); the nitrous esters (amyl nitrite, ethyl nitrite); and the substances which are converted into nitrites within the body; notably nitroglycerin and hydroxylamin.[1]

I. SUMMARY OF ACTIONS.

1. Paralysis of the vasoconstrictor mechanism, mainly peripheral.
2. Paralysis of the vagus center.
3. Slow paralysis of muscle of all kinds with which they come into direct contact.
4. Methemoglobin formation.

1. **Vasoconstrictor paralysis.**[2]— This is first noticed in the

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Study Materia Medica Lesson 36.

[1] *Hydroxylamin* (NH_2OH) is decomposed in the body into nitrate and ammonium. It produces the effects of both these substances (methemoglobin formation), convulsions, central paralysis (Lewin, 1889).

[2] Exercises 52 and 59.

skin of the face, in an area similar to that involved in blushing, but which may extend over the entire trunk to the ilium. The meningeal vessels undergo dilation at the same time. There is consequently redness of the face, heat and throbbing in the head, and headache.

These first effects resemble very closely an incipient asphyxia. There is also some hyperpnea and cyanosis. The temptation might arise to refer them to the methemoglobin formation; but the spectroscope fails to reveal such at this time. It can also be shown on lower animals that the nitrite ion has a toxicity of its own, aside from the asphyxia. The latter, however, contributes considerably to the picture of the intoxication.

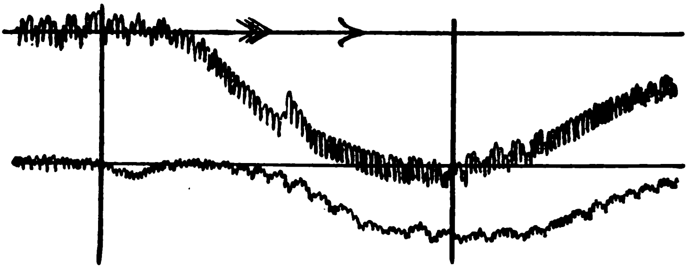

FIG. 83.—Amyl Nitrite on Carotid Pressure, Dog. The nitrite is inhaled between the two vertical lines. The upper tracing is taken from a normal dog, the lower after atropin. The heart was quickened by the nitrite in the upper tracing, but not in the lower.

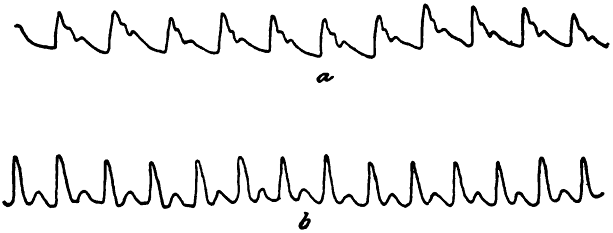

FIG. 84.—Amyl nitrite on sphygmogram: *a*, Normal; *b*, after inhalation of four drops.

This flushing lasts but a very short time if the action of the drug be discontinued. At the same time the *heart is greatly quickened,* so much so that a rise of blood pressure is frequently observed at this stage, the dilatation being more than overcome by the quickened beat. The dilatation does not, however, remain confined to the skin, but spreads over the entire body, and relaxation of the splanchnic area in particular causes a speedy *fall of blood pressure* (Fig. 83) and a dicrotic pulse (Fig. 84),

Mechanism of the Vasodilation.—*The fall of blood-pressure is due entirely to the vasodilation;* for it occurs equally well when the cardiac changes are excluded by atropin (Fig. 83). *The vasodilatation can be demonstrated* directly by inspection (the blushing); by plethysmographic measurements, by the increased rate of flow through vessels, etc. The dilatation occurs after destruction of the spinal cord and in excised organs; it occurs also after degeneration of the cervical ganglion. It is therefor due, at least in large part, to *depression of the tone of the vascular musculature.* (It seems useless, with our present knowledge, to discuss whether the action is on the muscles or endings.) The depression does not culminate in complete paralysis, for stimulation of the splanchnics still causes some rise.

If a nitrite is introduced into the cerebral circulation, and prevented from reaching the general circulation,[1] the blood-pressure does not fall. This indicates that *the cerebral centers do not play an important part* in producing the vasodilation. It is possible, however, that they are concerned in the blushing; for the peculiar distribution and prompt occurrence of this phenomenon points to a central origin.

The *pulmonary vessels* are also somewhat dilated, but not as much as those of the greater circulation. The pressure in the pulmonary arteries is therefore increased (Plumier, 1905).

2. The Tachycardia.—The vasodilation is generally accompanied by quickening of the pulse. This is due to a direct depression of the vagus center.

It is greatest in those animals in which the vagus is normally active, and small in others. (In the tracing of Fig. 83, for instance, it was slight, the vagus tone being low.) It is practically abolished by atropin.

The effect is due to the *direct action* of the nitrite on the vagus center; for it is obtained if the nitrite is confined to the cerebral circulation, and is absent if it is allowed to act on the general circulation, but prevented from reaching the brain.

It has been shown by experiments on excised mammalian hearts that the **cardiac muscle** is not affected directly by ordinary doses. (In pathologic conditions, an indirect effect may be produced by the relief of the heart from excessive resistance.) The excised frog's heart may be quickened by low concentrations (1 : 10,000); higher concentrations weaken (1 : 5,000), or stop (1 : 1,000) the contraction. This direct depressant action is also seen with toxic doses in mammals.

As the result of the quickening, *the excursions of the heart are smaller* The blood pressure waves appear particularly small, because the pressure wave is more readily dissipated, on account of the dilatation. The pulse, on the other hand, may be bounding, because the arteries are emptied more completely during diastole.

Another effect which may possibly be attributed to the central nervous system consists in a *quickening of the respi-*

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[1] To study the direct action of drugs on the brain, apart from their peripheral effects, the cerebral vessels are ligated and subjected to artificial perfusion with defibrinated blood, to which the drug is added.

ration. But this is perhaps only secondary to the changes in the circulation and blood.

Similarly, the variations produced in the secretion of *urine* appear to be purely secondary, and will depend upon whether the renal arterioles or those of the general circulation are relatively more dilated; the former causing an increase, the latter a diminution, of urine.

Convulsions are also sometimes noted, but they also may be secondary to the asphyxia.

3. This **asphyxia** depends upon the production of methemoglobin (or a mixture of this and nitric oxid hemoglobin). Nitrites differ from most other methemoglobin-formers in that the structure of the corpuscle is not destroyed. Consequently the only action is that of retarding oxidation, since methemoglobin parts with its oxygen much less readily than oxyhemoglobin. This may perhaps be responsible for the persistent glycosuria sometimes seen in animals. Methemoglobin, however, is not as stable a compound as is, for instance, CO; and when the tissues become actually O-starved, they can break up methemoglobin. It is consequently very difficult to kill animals in this manner, unless the nitrite be introduced more rapidly than the methemoglobin can be decomposed. If this is done, the animals may be saved by placing them in oxygen under pressure.

III. DIFFERENCES IN THE ACTIONS OF THE MEMBERS OF THE SERIES.

The principal differences concern *the rapidity and duration of the action.* Amyl nitrite, when inhaled, acts in 10 to 15 seconds, the action disappearing again within three minutes. Trinitrin, ethyl nitrite, and sodium nitrite act in two or three minutes, the action persisting a half to three hours. With erythrol nitrate, the effects appear only after fifty minutes, and last five hours.

The differences are to be referred to absorption; and with the organic nitrates, to the rate at which they are converted into nitrite. The *inorganic nitrates* (as KNO_3) are also reduced to some extent into nitrites in the body, sufficiently to produce methemoglobin if large doses are given; but they cannot be used therapeutically as substitutes for nitrites (Binz, 1901).

The *inorganic nitrites* are not much used, since they are quite irritant to the stomach (being decomposed by the gastric hydrochloric acid, with the production of the irritant HNO_2). Large doses cause fatty degeneration of the liver, similar to that produced by ammonium, and probably due to the formation of this substance. 60 to 70% of the nitrites disappear in the body, their exact fate being unknown.

Spirits of Nitrous Ether shows considerable alcohol action, and is used as a diaphoretic and diuretic more often than for lowering the blood-pressure.

Nitroglycerin has also a toxicologic importance, from its use as an explosive. *Toxic* doses cause vomiting, diarrhea, cyanosis, etc. Death occurs by respiratory failure.

Nitroglycerin is readily absorbed. Even the application of it to the skin causes some effect, and persons engaged in its manufacture suffer severely from headache during the first few days. After this, however, they appear to be quite unaffected, unless they leave work for several weeks and then resume the occupation. The work is said to be not unhealthful.

Smokeless gun-powders (nitroglycerin, nitrocellulose, etc.), when exploded, liberate gases which produce the combined effects of nitrites and asphyxia. The principal products are NO_2 (nitrogen peroxid) and CO (Kiefer, 1905). The vasodilation and tachycardia are followed by persistent headache ("powder-headache"), which does not yield to acetanilid, etc., but is best treated by strong coffee, and poultices applied to the back of the neck.

IV. DIFFERENCES IN SUSCEPTIBILITY.—UNUSUAL EFFECTS.

A remarkable tolerance for nitrites is often observed; this is sometimes only apparent, since the tablets decompose and often contain no nitroglycerin. The spirit is better, but also not quite stable. Other instances are authentic, and often due to acquired tolerance. D. D. Stewart (1905) reports such a case, in which 20 grains of absolute nitroglycerin produced only a slight effect. Some patients exhibit this tolerance from the start. Others respond very violently to small doses by alarming syncope with slow heart. The cause of this is not explained. The severity of the headache is similarly variable.

V. THERAPEUTIC USES.

The nitrites are used exclusively for their dilator action. This is indicated in:

1. *Excessive resistance* to the work of the heart (arteriosclerosis).
2. *Arterial spasms* (angina pectoris, some forms of migraine, asthma, cold extremities).
3. *Hemorrhage:* through lowering of general blood pressure.
4. In *toxic rise of blood pressure* (lead colic, barium, strychnin, digitalis).

VI. EXCESSIVE RESISTANCE TO THE WORK OF THE HEART.

This condition is shown by a high-tension pulse, with marked elastic oscillations but weak dicrotic wave.

A condition of this kind is dangerous mainly by reason of the extra work which it puts upon the heart. Such extra resistance is found especially in arteriosclerosis, also in *angina pectoris;* in *poisoning by* various drugs, such as Strychnin, Lead, Barium, or Digitalis; in *nephritis;* and a relative excess exists when the heart itself is weakened, as in *fever,* whilst the pulse may indicate a normal or even low blood-pressure.

When the rise of blood-pressure is due to a nervous contracture of the vessels, as in angina or with strychnin, the nitrites are certain to give relief, and preference is given to amyl nitrite on account of its quicker action. But when the lumen of the vessels is greatly narrowed by fibrous thickening of their walls, and the muscle has largely disappeared, the nitrites naturally cease to be effective. Nitrites are therefore useless in angina pectoris if this is due to coronary sclerosis; and in *arteriosclerosis* they are for the same reason of use mainly in the early stages, and then they only give relief without curing the disorder. But this relief is so marked as to make them of great value. It may persist for two or three weeks after the drug is discontinued.

When the resistance is not increased, but the heart is so weakened as to be unable to cope with it, as in fever, it must be remembered that these drugs cause a further lowering of blood-pressure; and when this is already dangerously low, they would generally be contraindicated. But when this is not the case,—that is, when the weakening has not progressed very far,—a temporary relief may be secured, and this often suffices to restore the heart to its normal vigor. It would, of course, be advisable in all such cases to combine them with drugs which increase the power of the heart, such as digitalis; and, *per contra,* the addition of nitrites to digitalis is useful in preventing the vasoconstriction caused by the latter. Another condition which calls for the use of vasodilators is valvular disease, in cases in which the cardiac muscle is incapable of being stimulated to increased force by digitalis — such as in fatty degeneration. In these digitalis does harm instead of good, and nitrites are used as a last resort, effecting relief if they do not contribute to a cure.

On account of their therapeutic effect, the vasodilators were called *Vascular stimulants* by the older authors, the "stimulant" referring to the system at large, not to the vessels. On account of the confusion to which the term leads, it should be entirely abandoned. The same authors usually speak of drugs producing vasoconstriction as "vascular tonics."

Amyl nitrite has been reported useful in certain obscure diseases: in epilepsy (especially when given at the time of the aura); in eclampsia; in hemicrania, etc. While it is often entirely without effect in epilepsy, it is of undoubted benefit in other cases, which are perhaps dependent on a vasomotor spasm of the vessels supplying the motor areas.

VII. MATERIA MEDICA.

Administration.— The dosage of the nitrites should be kept as low as possible, to prevent the rapid development of tolerance. It is best to give just enough to cause a slight quickening of the pulse, and feeling of fulness in the head. This dose may be given four times a day. The initial dose may be 0.6 mg. ($^1/_{100}$ gr.) of nitroglycerin, increasing gradually. The treatment may be intermitted for a few days in every two or three weeks, starting again with a smaller dose.

Amylis Nitris (U. S. P., B. P.).— Amyl nitrite.— A yellowish liquid of peculiar odor, containing about 80% of amyl (chiefly iso-amyl) nitrite, $C_5H_{11}NO_2$. Obtained by the action of HNO_3 on amyl alcohol. Insol. in water, freely miscible with alc. *Dose:* 1 to 3 drops, inhaled from a handkerchief (0.2 c.c. = 3 ♏., U. S. P.). It may be carried in thin glass capsules, "pearls," one of which is crushed in the handkerchief as needed.

Spiritus Ætheris Nitrosi (U. S. P., B. P.).— *Sweet Spirit of Nitre.*—

Study Materia Medica Lesson 37.

An assayed (4% U. S. P.; 2½% B. P.) alcoholic solution of Ethyl Nitrite ($C_2H_5.NO_2$). Made by acting on alcohol and sodium nitrite (U. S. P.; or nitric acid, B. P.) with sulphuric acid and distilling the product. Miscible with water or alc. *Dose:* 1. to 4. c. c. (¼ to 1 ʒ) (2 c. c. = 30 ♏., U. S. P.).

Liquor Ethyl Nitritis (B. P.).— A 3% solution in glycerinated alcohol. *Dose:* 1 to 4 c. c. (¼ to 1 drachm).

Sodii Nitris (U. S. P., B. P.).— $NaNO_2$. White crystals or pencils. Sol. in 1.4 water, slightly in alc. *Dose:* 0.03 to 0.3 Gm. (½ to 5 grs.) (0.065 Gm. = 1 gr., U. S. P.).

Spiritus Glycerylis Nitratis (U. S. P.) [*Liquor Trinitrini,* (B. P.)].— *Spirit of Nitroglycerin, Trinitrin, or Glonoin.*— An alcoholic 1% solution of $C_3H_5(NO_3)_3$. (Nitroglycerin is prepared by acting on glycerin with HNO_3 and H_2SO_4). *Dose:* 0.05 to 0.2 c. c. (1 to 3 drops) (0.05 c. c. = 1 ♏., U. S. P.).

Tabellæ Trinitrini (B. P.).— 0.6 mg. = $^{1}/_{100}$ gr.

* *Erythrol Tetranitrate.*— Colorless and tasteless crystals, soluble in alcohol, insoluble in water. Dangerously explosive. *Dose:* 0.01 to 0.05 Gm. (⅙ to 1 grain), in powders, tablets, or alcoholic solution.

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* Not official.

CHAPTER XXII.

DIGITALIS GROUP.

I. MEMBERS.

The distinguishing feature of this group consists in an increased tone of muscular tissue generally, manifested most conspicuously on arterial and cardiac muscle, leading to increased strength and duration of the systole, and to rise of blood-pressure.

This action is possessed by a large number of substances, of very different chemical structure, derived from widely separated families of plants, and also from the animal and mineral kingdoms. Only a few of these can be substituted for digitalis in therapeutics; the others have more pronounced side-actions and have mainly a scientific and toxicologic interest. The most important are:

1. *Non-nitrogenous Neutral Principles, Glucosids, and Resins.*— The active principles of *Digitalis* (Digitoxin, Digitophyllin, Digitalein, Digitalin); *Squills* (Scillitoxin); *Strophanthus* (Strophanthin); *Apocynum* (Apocynin and Apocynein). Of *less importance* are those of Adonis, Oleander, Helleborus niger, Convallaria, Cheiranthus, and others. A number of these and similar drugs enter into *arrow-poisons,* as Strophanthin, Ouabain, Antiarin, Acocantherin, etc.

The toxic principles found in the skin and blood of the toad (Bufanin and Bufotalin) have typical digitalis actions. They are closely related chemically to each other, do not contain nitrogen, and appear to be derived from cholesterin.

2. *Alkaloids.*— The most typical is *erythrophlein,* a glucosidal alkaloid. Other alkaloids show a very similar action, as veratrin, curin, epinephrin; pituitary extract and camphor also resemble digitalis in their cardiac actions. A digitalis action is also claimed for *Cactus grandiflorus,* but experimental and clinical reports on this drug are still very contradictory.

3. *Inorganic Substances.*— Barium salts, hydrates, and normal saline

solution possess cardiac actions which resemble Digitalis. The resemblance is perhaps only superficial, for it has been shown that the heart of toads is very tolerant to all typical digitalis poisons, but not to barium (Heuser, 1902). They have no therapeutic importance.

Digitalis is by far the most important member of the group, from the therapeutic standpoint; strophanthus being practically its only competitor. The latter was introduced into medicine by Fraser in 1885. The use of Digitalis is also comparatively recent; it was first published as a remedy in cardiac dropsy in 1775 by Withering of Birmingham. However, the drugs of this group were recognized as poisons, and employed in folk-medicine, long previously.

II. COMPOSITION OF DIGITALIS.

Digitalis contains a number of active principles (see table XI). These are as yet only imperfectly known, as it is difficult to isolate them in pure form. *Digitoxin* occurs in the largest amount and is the most important. *Digitophyllin* (present in the leaf, but not in the seed), *Digitalin* and *Digitalein* also possess the typical digitalis action; *Digitonin* belongs to the saponin group; it depresses the heart and dilates the vessels, but is not present in sufficient amount to seriously affect the action of the others; *Digitin* and *Digitoflavon* are practically inactive.

Solubility.— Digitalin, Digitalein, and Digitonin are fairly soluble in water. Digitoxin, Digitophyllin, and Digitalin are freely soluble in alcohol, but almost insoluble in water. However, when the plant is extracted with water, they are largely brought into solution by the digitonin; so that a 1 : 10 infusion contains two-thirds of the digitoxin of the leaf. Nevertheless, the *alcoholic preparations* are relatively richer in digitoxin, the *aqueous* in digitalein and digitonin.

Decomposition Products.— Like all glucosids, the digitalis principles decompose readily, especially in the presence of water and acids. The decomposition products are also imperfectly known. *Toxiresin*, from digitoxin, and *Digitaliresin*, from digitalin and digitalein, may be accepted provisionally. They are not present in good preparations of digitalis, but are formed when the drug is stored under unsuitable conditions; they occur also in old infusions. Their actions are typically those of the picrotoxin group. They seem to be more poisonous than the original digitalis principles, and have been blamed for some of the accidents occurring in the therapeutic use of Digitalis. The subject requires further investigation.

III. SUMMARY OF ACTIONS.

The members of the digitalis group produce a direct stimulation of all forms of muscular tissue; of the vagus

TABLE XI.—DIGITALIS PRINCIPLES.

SCIENTIFIC NAME.	QUANTITY IN LEAF.	SOLUBILITY OF THE PURE PRINCIPLE IN WATER.	ACTION.	COMMERCIAL PRODUCTS (IMPURE). (The scientific products are designated "verum.")	DECOMPOSITION PRODUCTS. Schm. = Schmiedeberg. K. = Kiliani.
Digitalin	Small or none.	Insoluble.	Cardiac stimulant and vasoconstrictor.	Digitalin amorphe Homocolle.	Digitoresin, Schm. Digitalignin } K. Digitalose } K.
Digitoxin	Largest.	Insoluble.	Cardiac stimulant and vasoconstrictor.	Digitalin cryst. Nativelli. Digitalin purum amorph. French and Belgian. Digitalin chloroformique.	Toxiresin, Schm. Digitoxigenin } K. Digitoxose } K.
Digitalein	Small.	Soluble.	Cardiac stimulant and vasoconstrictor.		Digitaliresin, Schm.
Digitonin (amorphous and crystalline)	Small.	Soluble.	Cardiac depressant and vasodilator.	Digitalin purum pulv. German. = 50-60% digitonin. Digitalin cryst, Merck.	Digitogenin. Digitoresin, Digitonein, Paradigitogenin.
Digitin	....	....	Inactive.		
Digitophyllin (only in leaves)	Small.	Insoluble.	Cardiac stimulant and vasoconstrictor.		
Digitoflavon (only in leaves)	....	....	Inactive.		

ganglia; and of the medullary centers; they also cause local irritation. These actions result in the following phenomena:

1. A direct action on the *cardiac muscle,* increasing its irritability and contractility, leading to more powerful systole, and later to lessened diastole.
2. *Vagus stimulation,* mainly by the increased blood pressure; but partly direct.
3. *Vasoconstriction,* mainly by direct action on the arterial muscle, but partly central.
4. A *diuretic action,* produced only in cardiac disease.

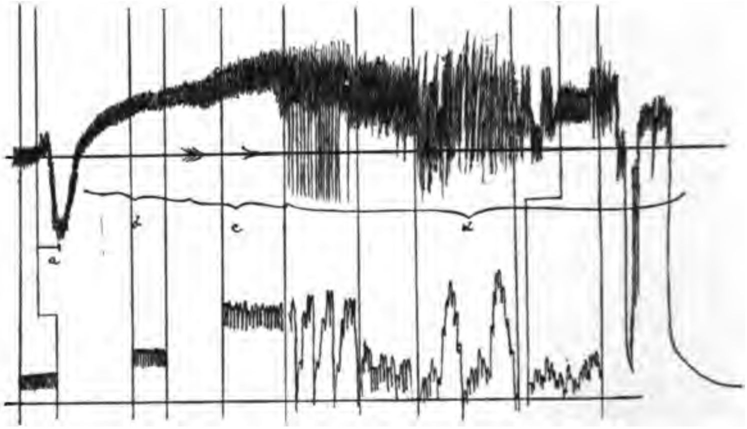

FIG. 85.—Digitalis on blood-pressure, dog. The upper tracing is taken on a very slowly moving drum, to show the successive effects. The lower tracing is taken with a faster speed. The vertical lines indicate the correspondence of the fast and slow tracings. The upper abscissa corresponds to the original mean pressure; the lower abscissa to zero pressure. The digitalis is injected at *a.* (See text.)

5. A *picrotoxin action:* stimulation of all medullary centers, followed by depression.
6. A *local irritant action,* progressing to inflammation.
7. A *veratrin action* on skeletal and smooth muscle.

IV. DETAILS OF ACTIONS.

Circulation.[1]—The effects of digitalis may be divided, especially in mammals, into two well-defined stages, the therapeutic and toxic. The typical phenomena of the two stages are shown in Fig. 85.

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[1] Consult Exercises 49 and 62.

During the intravenous injection of digitalis, the pressure falls sharply (*a*), on account of the local irritant action on the heart and vessels. This does not occur in the other methods of administration. The fall is not at all lasting.

The **therapeutic stage,** Fig. 85 (b and c), and Fig. 86b, is characterized by a considerable rise of pressure and a stronger and slower heart beat. If the digitalis action is produced rapidly, it may be seen that the rise precedes any change in the heart; it is therefore due largely to vasocon-

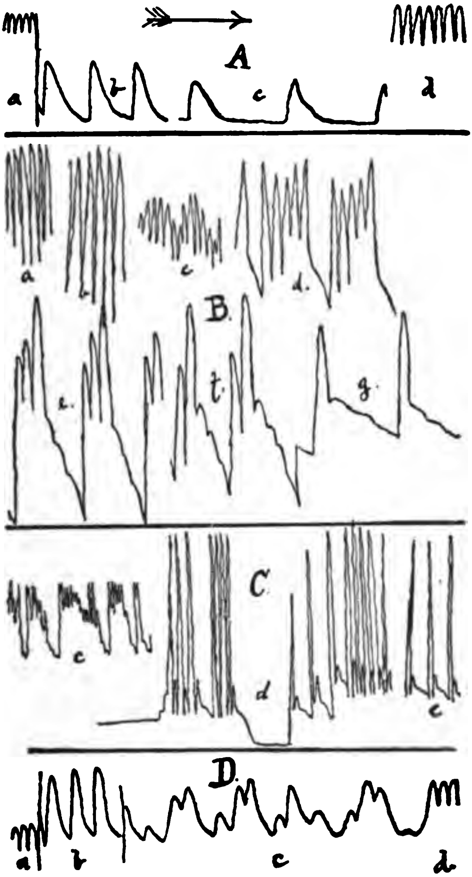

FIG. 86.—Blood-pressure tracings under digitalis, to show some of the types of irregularity in the toxic stages. A, B, C and D represent four different dogs. (*a*) is the normal tracing; (*b*) the therapeutic stage; the following letters represent the successive changes.

striction; and it can be readily shown that this is due largely to a direct action on the arterial muscle, although the vasomotor center is stimulated as well. The slowing is absent if the animal has received atrópin; it is at most very slight if the vagi have been simply divided. It is therefore due to central vagus stimulation (partly by the increased blood pressure, and partly by a picrotoxin action). The increased force of the heart beat is due in part to the vagus stimulation; but still more to the direct stimulation of the cardiac muscle; for it occurs also in atropinized animals. All the chambers of the heart participate in these actions; but the increase of force is greatest in the ventricles, particularly in the left.

During this stage, the systolic intracardiac pressure is increased; the heart is emptied more completely. If the heart is normal, the diastolic expansion is also increased. More blood is therefore thrown out at each beat, and also in a unit of time (notwithstanding the slowing). The pulse remains firm, even during diastole. Abnormal dilation of the heart is lessened, and irregularities tend to disappear.

The principal feature of the **toxic stage** is *extreme irregularity of the heart,* both as to strength and rhythm (Fig. 85 *d,* and Fig. 86).

The toxic action is often ushered in by a very slow rhythm (Fig. 86, *A, b,* and *c*), due to extreme central vagus stimulation. This is followed by a series of the most varied changes. *The heart-rate is generally increased.* The quickening is not due to paralysis of the vagus, for it occurs even in the excised heart, and the vagus responds to electric stimulation. It is caused by direct stimulation of the cardiac muscle.

However, the picture is apt to change from moment to moment. At times the beats are rapid and fairly small and regular, as in Fig. 86, *B c;* at others, they are extremely strong and slow, and the heart may stop completely for a time (end of Fig. 85 and during *d* of Fig. 86, *C*). This is evidently due to extreme vagus stimulation. More frequently, however, the variations concern the strength of the beat, rather than the rhythm.

One or more enormously strong beats are followed by very much weaker beats, sometimes quite imperceptible in the pulse, which is therefor *intermittent* (see Fig. 86, *B, e,* and *g*). These phenomena recur in groups, which remain fairly regular for a short time, but soon change to some other type, as may be seen in Fig. 86, *B* and *C.* These effects are sometimes due to respiration. In other cases, however, they are cardiac. They are also seen in the atropinized heart, and are mainly due to the *arythmia of the auricles and ventricles* (Cushny, 1899). It will be recalled that the ventricular contractions are normally originated by the auricular contractions. Toxic doses of digitalis seem to interfere with the transmission of this impulse, and at the same time, they raise the excitability of the cardiac muscle to such a degree that contractions can originate in the ventricles. The auricles and ventricles therefor beat independently; either may be the more rapid. As a consequence, the contractions will sometimes alternate, sometimes coincide, forming groups (see Fig. 87). If the auricular systole occurs during the ventricular diastole, the ventricles will be filled with blood when they contract, and the result will be a large pulse-wave; if the auricular and ventricular systole coincide, no blood will be moved, and there will be no pulse (see Fig. 87, *p*). This is the most satisfactory explanation of the group phenomenon. A further factor may come into play: it is probable that the auricular stimulus to the ventricle is not completely blocked by the digitalin. If the auricular and independent stimuli coincide, the ventricular contraction would be strong; if they interfere, the contraction would be weak or absent. This effect would support that previously described, and lead to the same kind of grouping.

Other occasional irregularities require a different explanation. These may coincide with respiratory variations, and indicate a rhythmic stimulation of the vagus and vasomotor centers (Fig. 85, *d*). It may also happen that the contractions follow each other so rapidly that the ventricle has not time to fill, and some of the contractions are therefor ineffective.

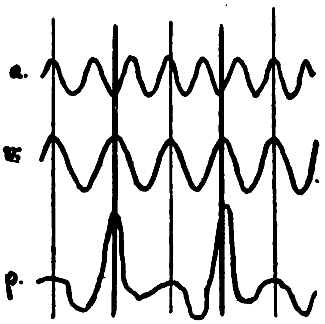

Fig. 87.—Diagram to illustrate the effect of auricular and ventricular arythemia; (*a*), auricular beat; (*v*), ventricular beat; (*p*), blood-pressure. The auricular systole precedes the ventricular at the heavy lines, and the pulse is consequently strong; it coincides at the light lines, and the pulse is weak. With this difference of rate (1 ventricular beat to 1½ auricular) each strong contraction will be followed by a weak contraction.

The **final phenomena of the toxic stage** also vary in different cases. Generally, the rate continues to increase, until *delirium cordis* results, and the heart stops in *diastole*. More rarely, death occurs by extreme vagus stimulation, as in Fig. 85.

The preceding description of the effects of the digitalis group on the circulation must be supplemented by a further study of some of the experimental evidence on which it is based. For this purpose, it will be well to take up separately the action on the muscle, vagus, and vasomotor system.

The direct effect of Digitalis on the Cardiac Muscle can be studied quite well on the *frog's heart.*[1] The phenomena are generally the same, whether the drug is applied directly to the exposed heart, injected into the lymph sac, or perfused through the excised heart by the Williams apparatus (see Exercises). They are not affected by atropin. Similar actions are produced on the nerve free heart of the embryonal chick. They are therefor purely muscular.

The effects are illustrated by Fig. 88 (*a*). The heart is slowed by lengthening of the systolic contractions, which are also more powerful. The output of the heart is at first increased. As the action progresses, the systole becomes longer and stronger, and the ventricle relaxes less and less during diastole, retaining a remarkably white appearance. The output is lessened. Finally, diastolic relaxation is abolished altogether, and the heart remains tonically contracted, in systolic standstill. It is not paralyzed, at this time, for if it be forcibly distended, it will beat again powerfully. Eventually, however, it will also fail to respond to this stimulus, but it remains in systole, which finally passes into rigor.

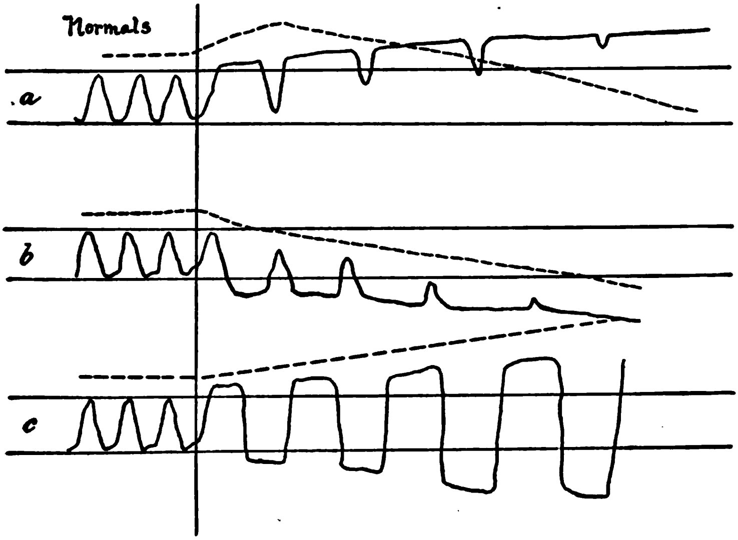

Fig. 88.— Diagram of Digitalis Actions. (*a*) On frog's cardiac muscle; (*b*) on vagus mechanism; (*c*) one of the possible combinations. Solid lines, ventricular contractions (upstroke = systole); dotted lines, blood-pressure and output.

The digitalis acts much more powerfully on the ventricle than on the auricle. The engorged appearance of the latter contrasts strikingly with the white, contracted ventricle. Arhythmia results, so that toward the end, the auricles make several beats to every ventricular contraction. They stop considerably *after* the ventricle.

Different parts of the ventricle also show a varying susceptibility. The apex is generally found in permanent systolic standstill when the base of the ventricle is still beating. Isolated areas or rings of permanent contraction may be scattered over the heart; the contractions may appear as peristaltic waves; the two halves of the ventricle may beat with different rhythm, etc. These peculiarities are referable to differences in the muscular susceptibility. If the vagus is not paralyzed, other irregularities may appear, owing to stimulation of the inhibitory apparatus. In intact animals, the heart occasionally shows a temporary diastolic standstill, from central vagus stimulation. Jacoby noticed that the external application of digitalis to the excised heart caused temporary diastolic standstill, the vagus terminations apparently being stimulated first.

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[1] Consult Exercise 49.

On account of its irritant action, the local application of digitalis may also cause a short primary quickening of the beat.

As has been said, the typical effects of digitalis are produced in the absence of nerves, and are therefor purely muscular. They are stimulant, for the heart contracts against a greater resistance; digitalis also *counteracts the effects of muscular depressants.* The prolonged and powerful systolic contraction shows that digitalis *increases the tone of the cardiac muscle,* somewhat as veratrin increases that of skeletal muscle. *The effect, as with veratrin, is exerted on all forms of muscle, cardiac, smooth, and striped,* and these two poisons have the greatest resemblance; with the difference that digitalis has the more powerful action of cardiac and smooth muscle, veratrin on the skeletal (Bottazzi, 1901).

As was explained under veratrin, poisons which stimulate muscle act first upon the rapidly contracting fibrillary substances, later upon the slowly contracting sarcoplasm. The smaller doses therefore cause a greater strength of the heart, with little change of rate; larger doses, stimulating mainly the sarcoplasm cause strong but slow contractions, with lessened relaxation; and very large doses fix the organ in systolic position. As with veratrin on muscle, maximal doses again paralyze the muscle entirely.

The Effect on the Excised Mammalian Heart (studied on Langendorff preparations by Hedbom, 1898; Braun and Mager, 1899; Gottlieb and Magnus, 1903) agrees with the frog's heart in the *increased strength of the systole;* however, *the rate is not slowed,* but usually quickened. Both ventricles participate in the action. The first effect consists in increased amplitude of the excursions; mainly of the systole. More blood is thrown out, and against a higher pressure. Any existing irregularities, and even fibrillation, are removed. The tonus increases. This corresponds to the *therapeutic stage.*

During the *toxic stage,* the heart becomes irregular. It may show a temporary diastolic slowing, due to peripheral vagus stimulation (this is therefor absent after atropin). This passes off, but the heart finally again becomes slowed and weakened, but now with a marked systolic tendency. Finally, fibrillary contractions develop, and the heart *stops in systole.*

In **Intact Mammals,** the cardiac actions are complicated by vagus stimulation and by the indirect effects of the changes of blood-pressure. It will be recalled that vagus stimulation slows the heart and increases the diastole; the effect is therefor the opposite of digitalis (see Fig. 88, b). When the two concur, as in the *therapeutic stage* of digitalis, the result is as in Fig. 88, *c; i. e.,* a slower beat, with much greater amplitude, systole and diastole being both increased. The output of blood is also increased, notwithstanding the slowing.[1] The auricles present the same effects. If the vagus stimulation is eliminated by atropin, the results are the same as in the excised heart, *i. e.,* increased systolic and lessened diastolic excursion, with slight increase of rate.

The irregularities of the *toxic stage* have been sufficiently discussed;

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[1] Exercise 53.

they are mainly of muscular origin, with the occasional intermixture of vagus effects. In the auricles, the inhibitory action tends to predominate, so that their efficiency is impaired. The output of the ventricles remains good for a time, and this, together with the vasoconstriction, maintains a high blood-pressure. However, when the irregularity or vagus stimulation becomes extreme, the efficiency of the heart is impaired and the pressure falls. This in turn interferes with the coronary circulation, especially since the coronary vessels participate in the vasoconstriction. The heart then succumbs to the combination of anemia and digitalis poisoning, *stopping in diastole.* (Systolic standstill of the mammalian heart is only possible if the coronary circulation is maintained, *i. e.*, in artificially perfused preparations.) It is important to bear in mind these *indirect actions of digitalis on the heart,* produced by the changes in the general blood-pressure and in the coronary circulation.

The Blood-Vessels.— Reference to Fig. 88 (*c*) will show that the cardiac actions, the increased output of the heart, produces a rise of blood-pressure. Some authors have been inclined to consider this an adequate explanation of the phenomenon. However, the pressure rises before the heart is altered (Fig. 85, *b*). This can only be explained by a vasoconstriction. This vasoconstriction is very important in the therapeutic use of digitalis. Its existence may be demonstrated directly in many different ways, perhaps most conveniently by measuring the volume of organs, or by observing the venous outflow. Both are markedly diminished by digitalis.[1] The effect occurs early and is very persistent.

Gottlieb and Magnus (1901) have investigated this action very thoroughly. They demonstrated that it is *mainly of peripheral origin*, for it occurs after destruction of the central nervous system, and even in excised organs. Dixon (1903) found that it can be produced even when the nerve endings are completely paralyzed by apocodein; the action is therefor *directly on the arterial muscle*, analogous to the other muscular effects of digitalis. It is difficult to decide whether there is *in addition a central vasomotor stimulation.* This is rendered probable by some rather sudden changes in the relative constriction of different areas; and by the demonstrated action of digitalis on other medullary centers.

The *vasoconstriction is most pronounced* in the *splanchnic area, the intestines, spleen, and kidney* participating in it very strongly.

In the intact animal, *the vessels of the periphery, the skin, extremities, and brain may even be dilated.* This dilation is not a direct effect of the digitalis, for the vessels of these organs are constricted if the digitalis is perfused through them directly. The dilation results from the displacement of the blood from the powerfully constricted splanchnic vessels into the less powerful peripheral vessels. This can be shown by ligating the splanchnic vessels before giving the digitalis: the peripheral vessels will then be constricted by the drug. Digitoxin, the most powerful constrictor of the group, may even cause constriction of the leg-vessels in the intact animal.

The dilatation is brought about partly mechanically, by the intermediation of the high blood-pressure. In part, however, it is a vasomotor reflex, for some dilation occurs when the leg is separated entirely from the body, with the exception of the sciatic nerve. This arrangement would of course entirely prevent the dilatation if it were due solely to the mechanical effects of the increased blood-pressure.

The *pulmonary vessels* are scarcely affected by the digitalis (Gerhardt, 1902); the pressure in the pulmonary artery rises (but not as much as in the aorta), mainly through the increased force of the heart (Plumier, 1905). The constriction of the *coronary vessels* is quite powerful in the case of digitoxin, and interferes somewhat with the cardiac stimulation. Strophanthin does not have this effect (O. Loeb, 1903).

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[1] Exercises 51 and 71.

Diuretic Action.— In normal individuals, digitalis has very little, if any, action on the secretion of urine. In heart disease, however, it has a remarkably strong diuretic effect, especially in the presence of effusions. The water and chlorids are especially increased, the other urinary constituents being but slightly altered.

The negative results on normal animals show that the effect is not due to a direct action on the kidneys. The diuresis coincides in time and duration with the cardiac effects, and is indeed secondary to the mechanical changes in circulation, which are of such a nature as to favor filtration.[1]

Most prominent amongst these favoring factors are the increased size of the pulse-waves; the increased output of the heart; the lessened venous pressure; and the hydremia resulting from the absorption of the effusions. These conditions cause a corresponding increase of urine filtration even in dead kidneys (Sollmann, 1905). The vasoconstrictor action of digitalis, on the other hand, tends to produce the opposite effect. The perfusion of digitalis through the excised kidney therefore lessens the urine. These opposing factors explain the varying action of digitalis on diuresis, in intact animals.

With toxic doses of digitalis, the constrictor effect predominates under all conditions, the urine being diminished or suppressed. The irritant action of digitalis may contribute to this result, for the scanty urine is often blood, and there are other evidences of a nephritic action.

With therapeutic doses, the favorable and unfavorable actions seem to balance each other, *in normal individuals,* since the quantity of urine is not changed. *In cardiac disease,* the conditions are peculiarly favorable to the beneficial effects: the cardiac action is then much larger, and the removal of the effusions and venous congestion can of course occur only in this disease.

The diuretic effect of digitalis may be improved by lessening the vasoconstrictor action. This may be accomplished by employing the less constricting preparations: the infusion of digitalis instead of the tincture (the former containing relatively less of the constricting digitoxin); strophanthus also has a comparatively small constrictor action; or the vascular action may be counteracted by the administration of nitroglycerin. In cardiac disease, digitalis is the most effective and the most persisting diuretic.

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[1] Exercise 69.

Picrotoxin Actions.— The stimulant effects on the vagus and vasomotor centers have been described. The respiratory center is also stimulated, but this effect is of very subordinate importance. The nauseating effects of this group are perhaps also partly medullary, but mainly local. Large doses would probably paralyze the medullary centers; but it is difficult to demonstrate this, as the digitalis produces more violent actions indirectly, through the circulatory changes. These probably account also for the inconstant effects on other nervous centers.

Local Action of Digitalis.— This is in the nature of an irritation. Digitalis has little action on the skin, its principal effect being on the mucous membranes. If taken internally in large doses, it gives rise to *gastritis and diarrhea.* This is of some little importance, as it may interfere with the use of digitalis in certain cases. It is usually taken as a sign to stop the digitalis, to safeguard against cumulative effects. The local irritant action is further of importance in that it interferes with the hypodermic administration of digitalis. In many cases this causes *abscess formation.*

Onset and Duration of Action; Cumulative Effect.— The action of the digitalis group is peculiar, in that it cannot be secured at once, unless toxic doses are given intravenously. If this is done, the animal goes through all the stages; but even in this case, several hours are usually required until death occurs, no matter how much of the drug is given.

When therapeutic doses are given, no effect whatever can be noticed for several hours; and the full action is only secured when the drug has been administered for several days. On the other hand, it persists for a week or so after the administration is stopped. This applies both to the cardiac and the diuretic, and probably also to the vasomotor action. In other words, *the effects of digitalis are cumulative.* If this very important fact is neglected, and the digitalis pushed to secure a more rapid action, the cumulative effect may result in the sudden development of the toxic stage. This stage, in which the pulse is quickened, may be mistaken for a failure of digitalis to act; and lead to the temptation to further increase the dose. This may indeed temporarily slow the heart, but it will inevitably hasten a fatal ending. In the therapeutic use of the drug, it is necessary to secure the cumulative effect; but great care must be exercised so that this does not exceed the therapeutic limit. The action of the drug should therefore be very carefully watched by the physician.

The mechanism of the cumulative action is not fully understood. It is known that the drug is absorbed and excreted very slowly; this may partly account for the phenomenon. Arrest of excretion through anuria may explain the sudden outbreak of the toxic effects in some cases. Further, the improvements caused by digitalis tend to be self-perpetuating, as will be described under the therapeutic uses. However, the long delay which precedes the actions when moderate doses are given intravenously to normal animals, indicates that the cause of the phenomenon lies largely within the muscle cells, *i. e.*, in their slow but prolonged response.

V. DIFFERENCES IN THE MEMBERS OF THE GROUP.

The atypical members — alkalies, veratrin, and barium salts — resemble digitalis only when they are used in small doses applied directly to the frog's heart. If used in larger quantities, they paralyze the heart muscle from the start — especialy the barium salts and alkalies — and produce diastolic standstill.

All these drugs have more powerful effects on other parts of the system. In the case of alkalies and acids it would be quite impossible to obtain a digitalis action by oral administration, for they would be neutralized before they reached the heart.

All the regular members of the digitalis series have the typical actions which have been described, but the extent to which they act upon the three systems — vagus center, cardiac muscle, and vasomotors)— differs in the different members of the group; and this is of great practical importance, because it limits their employment in several cases and makes one more useful than another. The subject has scarcely been sufficiently investigated experimentally, especially with regard to the effect upon the total circulation (as could be done by circulation time and similar methods). Therapeutically it is often found that one member will do harm, whilst another will prove beneficial.

The cardiac effects are fairly uniform; the differences concern mainly the other actions. Only the more prominent drugs can be considered, our knowledge of the others being too scanty. Digitoxin and erythrophlein have the strongest local and gastrointestinal action. Digitoxin is the most powerful vasoconstrictor, and shows the greatest tendency to cumulative action. The other digitalis principles possess these actions to a lesser degree; and strophanthus is the weakest in all these respects. Of the digitalis preparations, the tincture produces these side actions more powerfully than the leaf or the infusion. In scilla and euonymus, the local actions predominate so strongly, that the former is employed mainly as a nauseant, the latter as a cathartic. Apocynum agrees quite closely with digitalis (Wood, 1904).

The *local action* of digitoxin practically preclude its use hypodermically; digitalein may be administered in this manner. The *vasoconstriction* is very important, being sometimes desired, and sometimes harmful, especially when the diuretic action is wished. The *cumulative action* is produced by all members, but in a varying degree, as indicated above (Fraenkel, 1903).

VI. TOXICOLOGY.

The toxic effects of digitalis are important, since they may arise suddenly during the continued therapeutic use of the drug, even when ordinary doses are given. The *symptoms* have been described: nausea; vomiting; diarrhea; fast, irregular, intermittent, small pulse; and variable nervous disturbances. There are no characteristic *postmortem lesions,* except possibly some gastroenteritis.

As to the **treatment** of digitalis-poisoning, this should be mainly prophylactic — *i. e.,* directed to the avoidance of the cumulative action. This can be best done by intermitting the digitalis for several days at a time, and then giving it again for a few days, and so on. The dose should be cut down, not increased, when the pulse becomes rapid.

When the poisoning has actually set in, and there is reason to suppose that digitalis is still contained in the stomach, this should be evacuated. The rest of the treatment is purely symptomatic; general stimulants should be given, because the danger in digitalis-poisoning is mainly on account of its action on the medullary centers; or, at least, very little can be done for its action on the heart. If the blood-pressure is high, one may counteract the constriction of the vessels by nitroglycerin.

VII. THERAPEUTIC USES.

The first stage of the digitalis action is the only one intentionally induced for therapeutic purposes. In order to appreciate its indications, it will be well to recall its phenomena. These are:

1. Slowing of the heart, with systole and diastole both lengthened.
2. Increased strength of beat, leading to greater efficiency of the individual contractions, and to an increase in the total efficiency (greater outflow per unit of time and greater pressure). This effect is most conspicuous on the left ventricle, less on the right, least on the auricle.
3. A tendency to the systolic phase.
4. A rise of blood pressure, due mainly to the increased

action of the heart, but partly also to a vasoconstriction. In consequence of the latter, there is somewhat increased resistance in the circulation.

In consequence, digitalis is *indicated in all conditions of rapid pulse with low blood pressure.* It is especially useful in **valvular disease** of the heart by causing compensation, by preventing the reflux of blood, and by relieving congestion.

In order to understand the manner of its action in these conditions it will be well to briefly review the phenomena produced by these lesions on the simplest case, viz., **mitral insufficiency.**

The diagram (Fig. 89) will serve to illustrate these points. When an insufficiency of the mitral valve exists,—when this cannot close the auriculo-ventricular orifice,—the ventricular systole will not empty the entire contents of this chamber into the aorta; a part of the blood, instead of taking the normal path through the greater circulation, will be pumped to and fro between the auricle and ventricle. What will be the result? Following the direction of the stream, there will be throughout the circulation a lessened amount of arterial blood, which implies lessened nutrition. All the organs will perform their functions less thoroughly on account of this. The heart muscle will become weaker through the lessened coronary circulation. There will be a tendency to degeneration of its muscular fibers. The kidneys will secrete less urine. The anemia of the intestines will interfere with digestion and absorption. There will be a similar interference with the nutrition of the liver and with its functions.

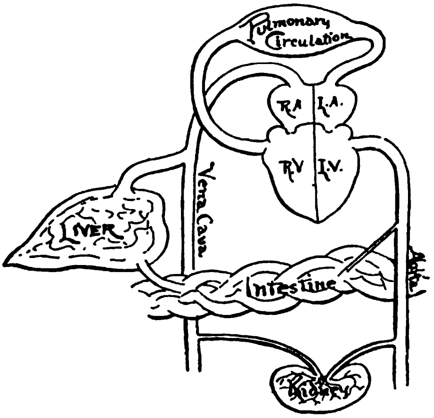

FIG. 89.—Diagram of circulation.

In the reverse direction, the regurgitation of blood from the ventricle into the auricle will oppose the emptying of the pulmonary veins. This produces congestion of the lungs; the amount of blood flowing through the lungs will be diminished, consequently less oxygen will be carried; so that the arterial blood, which, as we noticed before, was diminished in amount, will also be diminished in oxygenating power. This congestion of the lungs tends to pulmonary effusions and edema.

The passive congestion will not stop here, but extend to the right ventricle, to the right auricle, thence to the hepatic circulation, and to all the abdominal viscera. The venous congestion interferes with the nutrition and functions of the organs. (The function of the kidney can be entirely stopped by ligating the veins coming from it; and the urine flow varies with the rapidity of the circulation through the kidneys.) This venous congestion also leads to edema and effusion, just as does ligation of the veins.

The valvular defect therefore interferes with nutrition in three ways: By the lessened amount of blood thrown into the aorta; by the lessened oxygenating power; and by the venous congestion.

The heart is, perhaps, the first organ to suffer under these conditions. Consequently it will become weaker and weaker, and in becoming weaker it will render the conditions worse, establishing in this way a kind of endless chain, a *circulus viciosus.* Further, the edemas will interfere mechanically with the movements of the heart.

These are, in brief, the conditions which have to be met. This the heart itself attempts to do by hypertrophy, and as long as the hypertrophy is sufficient it is useless, and may even be harmful, to employ any drug. But let us suppose that, from any cause, the compensation has become insufficient. This may be from extra work thrown upon the heart, from an extra congestion through a cold, or from any other cause. As has been seen, even a temporary deficiency will lead to a continuous and ever-aggravating chain of symptoms, and herein lies its danger. This may be prevented by digitalis, or the chain, if already started, may be broken by it, and reversed. It will be remembered that the therapeutic action of digitalis results in stronger contractions of the heart, in prolonged phases of systole and diastole, and, in consequence, in a rise of blood pressure. If the heart contracts more strongly — and we take this to be the principal action of digitalis — a larger amount of blood will be thrown into the aorta and coronary circulation. The first effect will be an improved nutrition of the heart. This in itself will again cause the heart to contract more powerfully, and an endless chain of improvement will replace that of weakening. The tonic action — the fact that the digitalis tends to produce a permanent systolic condition — aids in this result in that it narrows the rings of the valves, brings them together, narrows the orifice, and in this way abolishes the effects of the distention and tends to lessen the insufficiency.

Since the heart pumps more blood, the whole arterial system will be distended and more blood will be forced through the vessels. In the case of the kidneys, this will lead to an increased secretion of urine; in the case of the intestinal organs, to improvement in digestion and absorption, and this to improvement in the general condition of the patient.

The venous congestion will tend to be relieved. This relief — as, in the reverse case, the drag — will fall in the first place upon the lungs, and bring about better oxygenation. The lowering of the venous pressure will tend to cause absorption of the effusions, and the heart, not being interfered with, will work more efficiently. The absorption of the effusions will render the blood more watery; and this, with the other actions of digitalis, will increase the elimination of urine; this in turn will facilitate the elimination of the effusions. So that, just as the heart went downward by the interaction of the different causes when compensation became insufficient, it will continue the improvement through the interaction of these same causes applied in reverse direction, once it is started on this track by digitalis. The oft-repeated stimulation of the cardiac muscle by digitalis also favors hypertrophy of the myocardium, even in normal animals (Wynn, 1904). For all these reasons, the results of digitalis are more or less permanent; they last even after the remedy has been stopped. All that is necessary is to re-establish compensation, and the heart may be relied upon under ordinary conditions to maintain it. After compensation has once been re-established, the employment of digitalis is contraindicated, from the fact that it causes constriction of the blood vessels. Relapse may, of course, occur through the same causes as primary insufficiency, and will then again require the drug.

The **vasoconstrictor action** of digitalis would seem to be an undesirable side action in its employment in cardiac disease; for it must increase the work of the heart, when it is desired to make this as light as possible. It must also interfere very seriously with the diuretic action. The less constricting members of the group, notably digitalein and strophanthus, have therefore been preferred by some; or the constriction may be counteracted by the simultaneous use of nitrites (which must be given much more frequently than the digitalis, since their action is less lasting). Clinical evidence is somewhat contradictory on this point; it seems certain that strophanthus sometimes fails when digitalis succeeds, and vice versa. It is quite possible that sometimes the increase of blood pressure is of more importance than the added resistance to the heart; whilst in other cases, the opposite is true. However, it seems fairly certain that the vasoconstrictor action is contraindicated when the cardiac disease is complicated by *nephritis*.

Other forms of insufficiency.— What has been said in regard to the action of digitalis on mitral insufficiency applies with equal force to insufficiency anywhere else in the circulation; for since the circulation is a closed system, it does not matter greatly where the additional force is applied or where the leak is — the result will in all cases be nearly the same. Digitalis is similarly useful in most cases of **stenosis.** The increased resistance in this case leads to the same results as the leakage in the case of insufficiency, and can be combated by the same method: viz., by strengthening the beat of the heart.

The only valvular disease in which digitalis may give unfavorable results is *mitral stenosis*. It will be remembered that digitalis acts comparatively weakly upon the auricles, much more strongly on the ventricles. Consequently a mitral stenosis cannot be affected by action on the left auricle, but only through the right ventricle. This increased work of the right ventricle, combined with the stenosis of the mitral valve, will tend to produce congestion of the pulmonary vessels, consequently to lessen the oxygenation of the blood, and in this way may interfere with the nutrition of the heart. Then, again, the systolic tendency of the digitalis will render the stenosis more marked, just as it counteracted insufficiency by approaching the valvules. On the other hand, the cardiac slowing will give the lungs more time to empty into the heart. Some conditions of the action of digitalis are therefore favorable, others unfavorable; and the effect upon patients is, in consequence, variable. Some cases of mitral stenosis are benefited by digitalis, others are even made worse. The digitalis must, therefore, be carefully watched, and if it is seen that the symptoms are not improved, it should be omitted and replaced by other remedies: If the symptoms arising from low blood pressure predominate, it would be well to employ vasoconstrictors; if those from a weakened heart, vasodilators.

Another condition in which caution in the use of digitalis is recommended is *aortic insufficiency.* It is said that in this condition the prolonged diastole will give the blood in the brain a chance to gravitate back into the heart, and thus produce syncope. It is difficult to say just how much weight can be placed on this. At any rate, it would justify the caution of keeping the patient in bed so as to avoid the upright position. No harm will be done by this; on the contrary, the rest can only be beneficial.

The occurrence of syncope on changing suddenly from the prostrate to the upright position is not rare, under the influence of digitalis, even with other lesions; the patient should be cautioned as to this. The mechanism of this phenomenon is obscure.

It must be remembered that the most useful effects of digitalis are produced by a stimulation of the cardiac muscle. As a result of the better nutrition produced in this manner, the muscular fibers may afterward hypertrophy, or new fibers may possibly be formed; but the primary action of digitalis itself is confined to the already existing muscle; consequently it will be of no use if there is practically no muscle left to respond to it. It is therefore useless with a heart which has undergone marked *fatty degeneration.* And in this condition it is even contraindicated, on account of the vasoconstriction. Probably the best treatment consists in the attempt to favor the oxidation and removal of the fat by carefully graduated exercise. Regarding the use of digitalis in *aneurysm:* the sudden distention of the aneurysmal sac by a larger mass of blood, which would be the result of digitalis, is exactly contraindicated. The only reason why digitalis has not done more harm in this way is that it has not generally been used in large enough doses to have a marked effect, Whilst the favorable action of digitalis on the heart is most pronounced in organic lesions, it has also a considerable value in *functional diseases,* arythmia, palpitation, etc., and when the heart is depressed by poisons. It will be recalled that these effects are also seen in animals.

Digitalis is sometimes employed in *fevers.* In a number of these — *e. g.,* in diphtheria — the heart is directly weakened in a manner which would be exactly counteracted by digitalis. Here, also, the vasoconstriction is contraindicated (unless there is also vasomotor paralysis, as is often the case). In certain fevers the heart is very much quickened, but without any weakening. These would not require digitalis, but rather aconite.

The **vasoconstriction** itself may be valuable in some conditions. In acute vasoconstrictor paralysis — as from shock — strychnin would be more useful, since it acts more quickly. Digitalis would only be preferred against more persistent vaso-paralysis, such as that producing one kind of dropsy.

The local actions are employed in very few members of the group: in the case of squills, as a diuretic and nauseant expectorant; and in the case of euonymus (wahoo), as a cathartic.

Admistration.— Digitalis is ordinarily administered by mouth, in the form of the tincture or infusion. 0.10 to 0.20 Gm. (1½ to 3 grs.) of drug [1 c. c. (15 ♏) of Tinct. = 8 c. c. (2ʒ of infusion] are given two or three times a day, continuing for ten days, then intermitting for four days, to avoid cumulative action. The dosage may be gradually diminished. The administration must be suspended if gastrointestinal symptoms occur, or if the pulse becomes fast, hard, and irregular. The patient should be seen at least daily. If the drug is not borne by the stomach, it may be used by enema (0.1 to 0.6 Gm. in 50 c. c. of water, once a day).

The therapeutic use of the *isolated digitalis constituents* has been strongly endorsed by some clinicians, whilst others do not favor them.

VIII. MATERIA MEDICA.

1. **Digitalis** (U. S. P.) [**Digitalis Folia,** B. P.].—*Foxglove.*— The leaves of the second year's growth of *Digitalis purpurea,* Scrophulariaceæ; Europe (and cultivated).

The activity of different commercial samples of Digitalis varies enormously. Of two lots under examination, one was *15 times* [!] as strong as another.

Digitalis leaves, cultivated in the United States, are fairly active.

Dose: 0.065 Gm. = 1 gr. (U. S. P.).

Other species of digitalis are also active.

Extractum Digitalis (U. S. P.).— The fluidextract evaporated to a pilular consistence. *Dose:* 10 mg. = ⅕ gr. (U. S. P.).

Fluidextractum Digitalis (U. S. P.).— Half-alcohol; miscible with water and alcohol. *Dose:* 0.05 c. c. = 1 ♏. (U. S. P.).

Tinctura Digitalis (U. S. P., 10%; B. P., 12½%); half-alcohol; miscible with water and alc. *Dose:* 0.3 to 1.5 c. c. (5 to 30 ♏.) 1 c. c. = 15 ♏., U. S. P.). Used mainly for cardiac action.

Infusum Digitalis (U. S. P., B. P.).— 1.5%. *Dose:* 4 to 15 c. c. (1 to 4 drachms) (8 c. c. = 2ʒ., U. S. P.). This preparation must not be boiled (boiling for three hours destroys the activity almost entirely). Used mainly for diuretic action.

2. **Digitalis principles:** On account of their expense and the insolubility of the greater number in water, they have not received extensive trial. It seems, however, doubtful whether they are at all superior to the galenic preparations. The "principles" on the market are for the most part prepared from the seed. They are generally impure mixtures.

Of the many that are sometimes recommended, the following may be selected:

* *Digitoxin* (verum).— Insoluble in water. *Dose:* 0.3 to 0.6 mg. ($^1/_{200}$ to $^1/_{100}$ grain).

* *Digitalein* (verum).— Soluble in water and alcohol. *Dose:* 1 to 2 mg. ($^1/_{64}$ to $^1/_{32}$ grain).

* *Digitalinum Germanicum* (mixture).— Soluble in water or alcohol. *Dose:* 1 to 2 mg. ($^1/_{64}$ to $^1/_{32}$ grain). (Large doses of digitalin (3 mg.) cause hyperpyrexia to 4° C. The cause of this is not known, but it may be due to a local action. Such doses would be dangerous.)

3. *Plants from Family of Apocynaceæ:*

Strophanthus (U. S. P.) [*Strophanthi Semina,* B. P.].— The ripe seed of *Strophanthus Kombé.* Central and western Africa (used by natives as arrow poison).. Strophanthin, etc.

Other species, some entirely devoid of glucosids or action, are sometimes substituted for these.

Tinctura S. (U. S. P., 10%; B. P., 2½%); two-thirds alcohol; miscible with water and alcohol. *Dose:* 0.3 to 0.6 c. c. (5 to 10 minims) (0.5 c. c. = 8 ♏., U. S. P.). Seems to deserve preference over Digitalis for all purposes.

Extractum Strophanthi (B. P.).— *Dose:* 0.015 to 0.06 Gm. (¼ to 1 grain).

Strophanthinum (U. S. P.).— A glucosid, or mixture of glucosids, obtained from Strophanthus. Most samples consist largely of pseudostrophanthin, which is nearly twice as active as the true. *Dose:* 0.3 mg. = $^1/_{200}$ gr. (U. S. P.).

Apocynum (U. S. P.).— *Canadian Hemp.*— The root of *Apocynum cannabinum.*

* Other species. North America.

Fluidextractum A. (U. S. P.).— Two-thirds alcohol, with glycerin.

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* Not official.

Study Materia Medica Lesson 38.

Miscible with water and alcohol. *Dose:* 0.3 c.c. (5 minims); as emetic, 1 to 2 c.c. (15 to 30 minims) (1 c.c. = 15 ♏., U. S. P.).

* **Oleander.**— Leaves of *Nerium Oleander,* Mediterranean. Oleandrin. Since this tree is often cultivated as an ornament, it may give rise to accidental poisoning.

4. *Family of Liliaceæ:*

Scilla (U. S. P., B. P.).—*Squills.*— The bulb of *Urginea maritima,* Mediterranean. Scillitoxin, etc.; mucilage. May be administered as * *Infusion,* 1 : 20. *Dose* of infusion: 1.5 to 5 c.c. (⅓ to 1¼ drachms).

Acetum S. (U. S. P., 10%; B. P., 12.5%).— *Dose:* 0.6 to 3 c.c. (10 to 45 minims) (1 c.c. = 15 ♏., U. S. P.).

Fluidextractum S. (U. S. P.).— Diluted acetic acid. *Dose:* 0.06 to 0.3 c.c. (1 to 5 minims) (0.1 c.c. = 1½ ♏., U. S. P.).

* *Infusion,* 1 : 20. *Dose* of infusion: 1.5 to 5 c.c. (⅓ to 1¼ drachms).

Tinctura S. (U. S. P., 10%; B. P., 20%); three-fourths alcohol. *Dose:* 0.3 to 2 c.c. (5 to 30 minims) (1 c.c. = 15 ♏., U. S. P.). Best preparation for diuresis.

Syrupus Scillæ (U. S. P., B. P.).— 4.5% (contains acetic acid). *Dose:* 2 to 4 c.c. (½ to 1 drachm) (2 c.c. = 30 ♏., U. S. P.); best preparation for nauseant.

Syrupus Scillæ Comp. (U. S. P.).— (Hive Syrup.)— Contains Antimony (see Index).

Oxymel Scillæ (B. P.).—10%. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

Pilula Scillæ Comp. (B. P.).— Contains Ginger and Ammoniac. *Dose:* 0.25 to 0.5 Gm. (4 to 8 grains).

Pilula Ipecacuanhæ cum Scilla (B. P.).— Contains 5% each of Opium and Ipecacuanha. *Dose:* 0.25 to 0.5 Gm. (4 to 8 grains).

Convallaria (U. S. P.).— *Lily of the Valley.*— The root of *Convallaria majalis;* Europe, cultivated. Convallamarin (digitalis action) and Convallarin (saponin action) (Pouchet and Chevalier, 1903).

Fluidextractum (U. S. P.).— Two-thirds alcohol. *Dose:* 0.3 to 1 c.c. (5 to 15 minims) (0.5 c.c. = 8 ♏., U. S. P.).

* *Extractum C. Florum Fluidum,* N. F.

* **Polygonatum.**— Solomon's Seal.

* *Smilacina.*— False Solomon's Seal.

5. *Family of Rannuculaceæ:*

* **Helleborus niger.**— The root; Europe. Helleborein, Helleborin. *The former is soluble in water (insoluble in alcohol) and holds forth promise for hypodermic administration. Dose:* Helleborus, 0.3 to 1.3 Gm. (5 to 20 grains); Helleborein, 0.01 Gm. (⅙ grain).

* **Adonis vernalis.**— Europe.

* *Adonidin.*— Soluble in water and alcohol. *Dose:* 0.005 to 0.015 Gm. (1/12 to ¼ grain).

6. *Other Families:*

* **Erythrophleum.**— The bark of *E. guineense,* Leguminosæ; Africa (Sassy Bark).

* *Tinctura E.*— 10%. *Dose:* 0.3 to 0.6 c.c. (5 to 10 minims).

* *Erythrophlein.*— Soluble in water or alcohol. *Dose:* 0.03 to 0.06 Gm. (½ to 1 grain).

Euonymus (U. S. P.).— *Wahoo.*— Root-bark. *Euonymus atropurpureus,* Celastrineæ; North America. * Other species. *Dose:* 2 to 4 Gm. (½ to 1 drachm).

* Not official.

Extractum Euonymi (U. S. P.).— Powdered; four times as strong of the fluidext. *Dose:* 0.1 to 0.3 Gm. (2 to 5 grs.) (0.125 Gm. = 2 grs., U. S. P.).

Fluidextractum Euonymi (U. S. P.).— Four-fifths alcohol. *Dose:* 0.5 c. c. = 8 ♏. (U. S. P.).

**Elixir E.,* N. F.— 15%. *Dose:* 15 c. c. (½ ounce).

**Euonymin.*— *Dose:* 0.03 to 0.2 Gm. (½ to 3 grains).

Euonymus preparations are used as purgatives.

* Not official.

CHAPTER XXIII.

ERGOT AND SAPOTOXIN GROUPS; SUMMARY OF TREATMENT OF COUGH.

(A) ERGOT GROUP.[1]

I. THE COMPOSITION OF ERGOT.

The composition of ergot is even more obscure than that of digitalis. It contains at least three active substances, with distinct actions; but these are difficult to isolate, since they are amorphous, and devoid of well-marked chemic characters. Moreover, they are very unstable.

Kobert (1884) named these principles: (1) *ergotinic acid* (*sclerotinic acid*), a nitrogenous glucosid possessing an action similar to that of sapotoxin; (2) an alkaloid *cornutin,* which has a convulsive action similar to picrotoxin, and a veratrin action on muscle; (3) a resinous non-nitrogenous principle, *sphacelinic acid,* responsible for the gangrene and uterine effects.

Jacobj (1897), whose conclusions are now generally accepted, agrees to the ergotinic acid and cornutin of Kobert; but it would seem that this cornutin is a mixture of alkaloids. Jacobj also found another alkaloid, *secalin,* which in itself is inactive. The sphacelinic acid of Kobert is found to be a mixture. He isolated from it two elementary principles: *sphacelotoxin* and *ergochrysin.* These do not exist in the drug in a free state. The sphacelotoxin exists combined with ergochrysin as "Chrysotoxin"; with secalin, as "Secalintoxin." The following table will serve to make clear our present knowledge of the Ergot principles:[2]

In the crude drug, these principles decompose very readily; the activity is very materially diminished when the drug has been kept a year, and it must therefore be renewed annually. The extracts of ergot, when carefully prepared

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[1] The introduction of Ergot into Therapeutics appears of fairly recent date. The first mention of its use is found in the sixteenth century.

[2] Vahlen (1904) has isolated a water-soluble product, *Clavin,* which is claimed to cause uterine contractions, but not convulsions or gangrene.

TABLE XII.—COMPOSITION OF ERGOT.

(Inactive in brackets.)

		Kobert.	Jacobj.	Jacobj.
			Primary Constituent.	Loose Compounds.
Nitrogenous Glucosids.	Concerned in Sapotoxin Action.	*Ergotinic Acid:*[1] nitrogenous glucosid. Sapotoxin action.	Accepted.	
Alkaloids.	Concerned in Convulsant Action.	*Cornutin:*[2] alkaloid of convulsant action (probably not a single substance).	Accepted. [*Secalin*, inactive.]	
N-free Resins.	Concerned in Gangrene Action.	*Sphacelinic Acid:* N-free resinous mixture with gangrene action (is a mixture of the active substances of Jacobj).	*Sphacelotoxin:* N-free resin, true active gangrene substance. [*Ergochrysin:* N-free inactive resin.]	*Chrysotoxin* active. = Ergochrysin + Sphacelotoxin. *Secalintoxin* active. = Sphacelotoxin + Secalin.

from the fresh drug, seem to keep much better; however, many worthless preparations are found on the market. These can only be discovered by physiologic tests, *i. e.,* the blackening of the comb of a rooster.

II. SUMMARY OF ACTIONS OF ERGOT.

Notwithstanding the radical differences in the actions of the separate principles of ergot, practically all samples of the drug produce similar effects, namely, those of sphacelotoxin. This evidently predominates over the other constituents. These actions may be summarized as follows:

1. *Stimulation of unstriped muscle,* partly central, but

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[1] Sclerotinic Acid.

[2] Ergotinin.

mainly peripheral, the action being exerted on the ganglionic cells or preganglionic endings. This in turn produces:

2. *Contractions of the Uterus,* especiallly when pregnant (leading to abortion); these are intermittent with small doses, tonic and persistent with large doses.

3. *Vasoconstriction,* differing in extent in different areas. especially powerful in the pulmonary vessels.

4. With large doses, and in susceptible animals, this leads to *gangrene,* especially in peripherally situated organs.

5. When rapidly injected, a primary depression and secondary stimulation of the *cardiac muscle.*

6. *Vomiting* and *increased peristalsis.*

7. The changes of circulation lead to affection of the *central nervous system.* These are necessarily variable, and are further complicated by a direct depressant action of sphacelotoxin, and a medullary stimulation by cornutin.

8. Large doses *paralyse the vasoconstrictor endings.*

The actions on the uterus, intestine, and central nervous system are seen in all animals. The effect on the blood-pressure is more variable; the gangrene is only produced in a few susceptible species.

III. DETAILS OF ACTION.

Uterus.— The action is sufficiently indicated in the summary; it can be induced after the nervous connections of the organ are severed, so that it is at least partly peripheral. When administered, in appropriate doses, near the end of pregnancy, it leads to a normal expulsion of the fetus, without injury to mother or child. It is therefore largely employed in obstetrics. When it is used earlier in pregnancy, much larger doses are required. These produce a tetanic spasm, a systolic tetanus, of the uterine muscles, which may even prevent the expulsion, and may terminate in rupture of the viscus; they are almost certain to asphyxiate the fetus. The uterine action is also utilized to prevent or check postpartum hemorrhage; the prompt contraction of the muscle closing the uterine sinuses.

Blood-Pressure.[1]— The circulatorv effects of ergot in mammals vary with conditions. When the drug is taken by mouth, or injected hypodermically, it causes a rather short and insignificant rise. If the injection is made intravenously, this rise is preceded by a much larger, short fall.

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[1] Exercise 59.

The rise on ***hypodermic injection*** amounts in animals to but 10 or 20 ♏♏. of mercury, and persists for only a few minutes; it is often entirely absent. It is too small to decide the site of its production. Intramuscular injection, and probably oral administration produce the same results. (It is possible that the rise is somewhat larger and more persistent in man, but this cannot be affirmed).

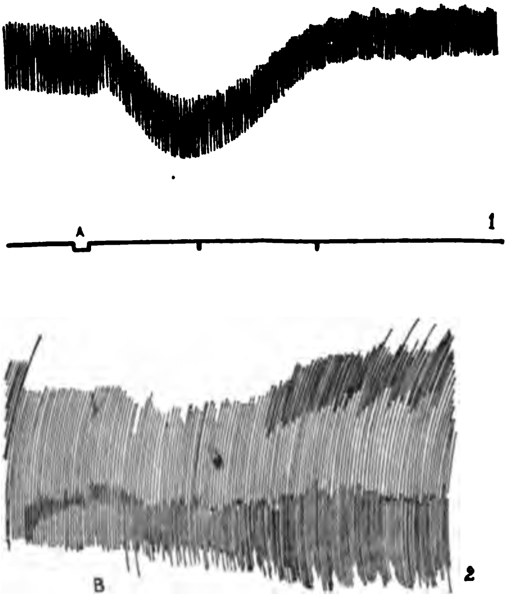

FIG. 90.—Ergot on blood-pressure (1) and heart (2); Dog. (½ natural size.) The abscissa corresponds to zero blood-pressure. Intravenous injection at A = B. The time-marks equal 15 seconds. The strength of the heart corresponds to the blood-pressure.

When the injection is made ***intravenously***, the rise is about the same, but it is preceded by a short but severe fall of pressure (50 to 60 ♏♏.). This fall is very constant and characteristic (Fig. 90). The figure indicates that the blood-pressure changes are mainly cardiac. Oncometric experiments prove that the fall of pressure depends purely upon the primary (apparent) cardiac depression; whilst the secondary rise involves two factors: a secondary stimulation of the heart and a vasoconstriction. These play a variable rôle, the constriction being especially variable; in exceptional cases, it may raise the pressure by 40 to 70 ♏♏.; but always very briefly. There is some evidence that the vasoconstriction is produced largely by stimulation of the center. It seems to be more pronounced and more peripheral in the pulmonary vessels.

The cardiac actions are also seen in the artificially perfused, excised heart; they are therefor purely peripheral.

The effects of ergot on the circulation are subject to considerable individual variations; they are very much diminished if the animal has a low blood-pressure. Different preparations of the drugs also vary, the primary fall of pressure being emphasized in some, the rise in others. The *age of the ergot* does not seem to modify its vascular effect, whilst it destroys its uterine action.

Very large doses of ergot paralyze the vagus center, and the vasomotor endings (adrenalin becoming ineffective, whilst barium is still active) (Sollmann and Brown; Dale, 1905).

Gangrene Action.— Whilst the action of ergot on most blood vessels is insignificant, it produces a very powerful and prolonged constriction of peripherally situated vessels in a few susceptible animals. The action is so strong that the blood stream is almost arrested; and if the poisoning is frequently repeated, or chronic, it produces thrombosis, hyaline degeneration of the vessel walls, and gangrene.

These effects can be best studied on the *comb of the rooster*.[1] In about an hour after giving the drug, the tips of the comb become cold and dark, even black, as if frozen. The effect persists for several hours, but has generally disappeared on the following day. If the ergot is given repeatedly, the darkening remains permanently and gradually involves the entire comb and the wattles. Eventually, these appendages undergo gangrene and may drop off. The extremities may also be involved; in one experiment, the entire wing fell off after a few days. Different roosters are unequally susceptible to these effects; in some, the comb may even blanche. (Similar changes in the comb may be produced by very large hypodermic doses of cane-sugar, piperazin, cantharidin, or chromic acid. All these produce profound changes in the circulation.)

Pigs are quite susceptible to the gangrene action of ergot. They react especially by pustular eruptions on the skin; the ears are particularly susceptible. *Horses and cattle* show similar changes. *Man* is quite subject to the gangrene, which begins in the extremities. The fingers, toes, or an entire member may slough off. *Dogs and Rabbits* do not seem to be susceptible to this action.

The cause of the varying susceptibility has not been demonstrated. It may be due to physiologic peculiarities, or merely to anatomic differences. The gangrene always begins in those situations in which the circulation is weakest. It differs in no essential from gangrene produced by any other cause. It may be dry or wet, according to whether liquifying bacteria are absent or present.

Alimentary Canal.— The same stasis is found in the vessels of the *alimentary tract*. It leads here to irritation, and in very advanced stages to ecchymosis, ulcer formation, etc. The ulcers involve particularly the lymph follicles, in which the blood supply is poorest. The stasis may lead to effusion of blood into the lumen of the intestine. The irritation combines with the direct muscular action of the ergot to produce violent *vomiting and peristalsis*. The appetite is lost. This action on the alimentary canal is also most marked in the animals mentioned, but occurs in others. The *liver* of roosters shows peculiar degenerations, resembling amyloid.

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[1] Exercise 51 (Grünfeld, 1892).

Central Nervous System.— This is affected both directly and indirectly, and the effects are correspondingly variable With moderate doses, the flow through the cerebral vessels is increased. Small doses may cause medullary stimulation (vagus-slowing; increased respiration, convulsions, etc.) through the cornutin. The sphacelotoxin seems to be purely depressant, so that large doses of ergot cause *death* by medullary paralysis. It has a narcotic effect for roosters.

IV. ACTIONS OF THE ISOLATED PRINCIPLES.

As has been stated, the effect of the ergot and its ordinary preparations correspond practically to those of **sphacelotoxin** and its compounds.

Chrysotoxin (Dale, 1905) in *moderate doses,* stimulates all varieties of plain muscle, whatever the source of their innervation. It causes a large and prolonged rise of blood pressure; the heart is slowed and strengthened; the pupils are at first dilated, then constricted. The small intestine, urinary- and gall-bladder are at first inhibited, then augmented. The uterus contracts strongly. The vasoconstriction is not prevented by destruction of the cord, but is abolished by nicotin, indicating its ganglionic origin.

Large doses paralyze the sympathetic endings in the blood vessels and other situations, so that they do not respond to epinephrin, which then produces vasodilation.

Cornutin seems to act almost purely on the *medulla,* its effects resembling those of picrotoxin. Its injection raises the *blood-pressure,* especially during the convulsions. This action is central. It does not produce the preliminary fall noted with ergot. It has no direct action on the *heart,* but a *veratrin effect* on skeletal muscle.

The statement is often made, particularly by pharmaceutic chemists, that the alkaloids are concerned in the *gangrene and uterine actions;* but this is denied, on sufficient grounds, by all competent pharmacologists who have investigated the subject. The apparent results are probably due to traces of the resins (Santesson, 1902).

Ergotinic acid has a typical sapotoxin action. Taken by the mouth it produces no effects beyond *local irritation,* as sapotoxins are not absorbed. If injected subcutaneously or intravenously, it will produce paralysis of the central nervous system and of protoplasm generally. It causes a peripheral paralysis of blood-vessels, and thereby lowers the blood-pressure.

V. TOXICOLOGY.— CHRONIC ERGOT.— POISONING.

Acutely fatal poisoning by ergot is rare in man. More commonly, the intoxication runs a protracted course, even when it is produced by a large single dose. The phenomena, then, agree with those of **chronic poisoning.**

This chronic poisoning by ergot, "*ergotism,*" was formerly very frequent endemically in consequence of the presence of ergot in flour. Ergot is a fungus which grows upon rye; and if special precautions are not taken to destroy it, it is very apt to become mixed with the grain in threshing and is ground up with the flour. In this way the population of large tracts of country have been poisoned. The last large epidemic in the United States occurred in New York in 1825. Since the cause has been recognized these epidemics have been less frequent, but in Russia they still play quite an important rôle (Schmack, 1897).

This chronic ergot-poisoning may take very *different forms* — forms which, upon superficial examination, bear almost no resemblance to one another. They were at one time classed as separate diseases. The difference is explained very readily when the different actions of the constituents of ergot are taken into account, and the fact that they may act partly on the blood-vessels and partly directly on the central nervous system. Changes which depend upon the circulation may occur almost anywhere in the body; they may appear first in one part, and later on in another, and this without definite order. The symptoms will be correspondingly variable. The initial stage is practically the same for all the different types of ergot-poisoning. From this initial stage two principal forms diverge: the convulsive form and the gangrenous form. Toward the end the symptoms again become similar in both forms.

The **initial stage** is ushered in by *disturbance of the* **peripheral sensory apparatus.** There is *formication* in the skin and various other disturbances of cutaneous sensation. *Hyperesthesia and anesthesia* exist at the same time in different parts, or even in the same part, the skin being hyperesthetic to some forms of stimulation and anesthetic to other forms.

These disturbances of sensation *begin at the extremities and spread upward.* This distribution favors the view that they are manifestations of changes in the circulation, since these would make make themselves felt first of all in the extremities. The disturbance in sensations also involves the **alimentary canal.** There is apt to be at once *voracious hunger and loss of appetite.* Digestion is much impaired on account of the disturbed circulation. Diarrhea and vomiting are very common. The vomiting is partly due to the disturbed circulation and partly to the action of the cornutin on the center. The **central sensory apparatus** also shows changes at this time. There is violent and persistent headache and central disturbances of the *special senses.* The **motor system** also begins to show abnormal symptoms, such as *twitchings* and tremors, most marked in the extremities and in the tongue.

In all these effects of ergot it is extremely difficult to say to what extent the phenomena are caused by the central, and to what extent by peripheral, actions. They are all largely dependent on disturbances in circulation, and these may in some cases be more prominent in the central nervous system; in others, peripherally.

At this point the sensory symptoms have reached their acme, and do not become any worse, but persist as they have been described. But the motor phenomena go on increasing; the twitchings pass into *spasms,* and then into permanent and often very painful *contractures.* Always beginning at the extremities, they involve the terminal phalanges of the fingers and ascend to the other joints. The facial muscles also participate. The type of these contractures shows that their origin is central. They are not absolutely persistent, but last for about half an hour; then pass off for a time, and reappear. This is very different from spasms of peripheral origin, such as those of lead-poisoning. The smooth muscles may also participate in these contractures; especially that of the bladder; so that there may be involuntary evacuation of the urine, *tenesmus,* etc.

The **pulse** is always *hard and small,* pointing to a high blood pressure. Its frequency, however, is variable. It is usually slow, due probably directly to the high pressure and to the cornutin action.

So far the symptoms, the initial stage, are common to all the different forms of ergotism; they can be accounted for partly by the change in the circulation and partly by the direct action of the ergot principles themselves. In the **second stage** the circulatory disturbances become more marked. The phenomena already seen — the disturbances of sensation and the contractures — persist; but to these are added secondary effects due to the prolonged slowing of the circulation. These may be most marked in the central nervous system or in the extremities. The former give rise to the so-called *spasmodic form* of ergotism. The predominance of stasis in the extremities produces the *gangrenous form.*

Why one action should predominate in some individuals, and another action in others, cannot be explained. Perhaps there may be some differences in the anatomic arrangement of the blood-vessels or extent of the innervation.

(A) The gangrenous form may have been indicated somewhat earlier. *Pustules* may have formed in the skin, which are due to this defect of circulation. In more marked degrees it affects the extremities. The entire member may be involved in the gangrene, which differs in no respect from any other gangrene; it has its line of demarcation, and may be *wet or dry* according to bacterial infection. The finger, toe, or limb may slough away without bleeding.

(B) In the **spasmodic form** the contractures pass into *tonic* and *clonic convulsions* or *epileptiform spasms.* Since any part of the central nervous system may be affected, the exact symptoms may be extremely variable. It may be repeated that they are due to a defective circulation in the central nervous system, which leads to stimulation and then to paralysis. Both forms, the gangrenous as well as the spasmodic, are therefore due to changes in circulation, and are determined by the sphacelotoxin and its compounds, the cornutin taking no part. The continued administration of cornutin does not produce in any animal symptoms resembling ergotism.

In acute ergot-poisoning — *i. e.,* where an overdose has been taken — the symptoms resemble very closely those produced by chronic ergotism, with the exception that they follow each other much more rapidly. They consist in vomiting, diarrhea, and constipation, disturbances of sensation, motor disturbances, epileptiform convulsions, and later gangrene. In the acute form it is, of course, possible, and in fact likely, that the cornutin plays a part in the production of the convulsions.

The **treatment** of ergot-poisoning cannot be anything but symptomatic.

VI. THERAPEUTICS.

1. The most important property is the effect upon the **pregnant uterus**; that is to say, the setting-up of the peristaltic waves, and later on, of tetanic contraction. This has led to its use to produce *abortion.* The dose required is quite large, however; and on account of the uncertainty of ergot preparations, it is a very dangerous drug for this purpose. The action on the uterus may be too strong and it may produce rupture; or general poisoning may result.

It has been recommended in delivery at term. In this case the required dose is much smaller, and consequently it can be used much more safely. However, it seems that the temptation to give large doses is still too strong, and whenever it is used in the early stages of labor it is apt to put the uterus into tonic contraction. It is not possible to say at present whether this is due to a specific effect of ergot on the human uterus or whether too large doses are always employed. The tonic contraction of the uterus at this time may actually interfere with the delivery of the fetus; and it may also produce asphyxia of the child by too strong contraction of the uterine vessels, or pressure on the cord. If it is used at all in this stage, the dose must be small. This is very important to remember.

The principal use of ergot is to stop **postpartum hemorrhage.** It is given here at such a time that its main action will appear after the placenta is delivered. If the hemorrhage is very large and a quick action is desired, it may be injected into the gluteal muscles. It acts mainly by producing rapid contraction of the uterine muscle, in this way obliterating the open sinuses.

It has been attempted to obtain ergot preparations which are more stable and more certain in their results than the ordinary extracts. Chrysotoxin (the combination of Ergochrysin and Sphacelotoxin) has been suggested, since it keeps for years without decomposition. But so far it has not been put upon the market, probably because the yield is quite small.

2. The supposed **vasoconstrictor action** of ergot has led to its use in a variety of conditions, where the circulation is supposed to be deranged.

This use cannot be based on the experimental data, for according to these the effect is too slight to be of any value — certainly much less than reflex stimulation. It is of course conceivable that, through the selective action of the drug, some areas are affected much more powerfully than the general blood-pressure would indicate. It is also possible that the effects on man are much more powerful than those on the dog or rabbit; but it is useless to indulge in these speculative explanations until the clinical results from the drug have been confirmed by a larger number of competent observers.

Ergot has been especially recommended in **pulmonary hemorrhage.** Clinical results are here of little value since the conditions tend to cease spontaneously. According to the experimental results, the drug is precisely contraindicated, for it raises the pressure in the pulmonary vessels. Its use in *hemorrhage* in other situations is equally devoid of rational foundation (Bradford and Dean, 1894).

The reported favorable effects of ergot in *asthma* may perhaps be attributed to its counteracting a pulmonary vasodilatation.

VII. MATERIA MEDICA.

Ergota (U. S. P., B. P.) (from the French "*Ergot,*" a cock's spur).—(*Secale cornutum.*)—A fungous growth (the sclerotium of *Claviceps purpurea,* Hypocreaceæ) from Rye.

Generally collected in Russia or Spain. Should not be older than one year. Constituents, see page 500; also fatty oils, proteids, and other extractives. Peculiar, characteristic odor. *Dose:* 2 Gm. = 30 grs., U. S. P.

The preparations are often injected *hypodermically* or intramuscularly, the fluidextract or an aqueous of the extract solution being used.

Fluidextractum Ergotæ (U. S. P.) [*Ext. Ergot. Liq.,* B. P.].—Acidified dilute alcohol. *Dose:* 2 to 4 c. c. (½ to 1 drachm). As yet the most satisfactory preparation. (2 c. c. = 30 ♏., U. S. P.)

Extractum Ergotæ (U. S. P., B. P.).—Various preparations are found on the market under the names of "Ergotin," etc., but they possess no advantage over the official product.

The U. S. P. Extract is a soft preparation, of eight times the strength of the fluidextract. It is in the main an aqueous extract, prepared by exhausting ergot with ⅔ alcohol, evaporating the alcohol, filtering, precipitating the filtrate with acid, again filtering, neutralizing, evaporating and adding some glycerin. *Dose:* 0.2 to 0.6 Gm. (3 to 10 grs.) (0.25 Gm. = 4 grs., U. S. P.).

Injectio Ergotæ Hypodermica (B. P.).—30% of extract. *Dose:* 0.2 to 0.6 c. c. (3 to 10 minims).

Iufusum Ergotæ (B. P.).—5%. *Dose:* 30 to 60 c. c. (1 to 2 ozs.).

Tinctura Ergotæ Ammoniata (B. P.).—25%. *Dose:* 2 to 4 c. c. (½ to 1 drachm).

Two other drugs which, in the absence of more definite knowledge, may at present be counted under the Ergot Group are Corn Smut and Cotton Root Bark.

* **Ustilago Maydis.**—Corn Smut.—A fungus analogous to Ergot, found on the corn-plant. Little is known about its composition or action, although it has been employed by the negroes for abortion, and stock-raisers have also observed that it has an ecbolic effect. Kobert states that it does not produce the ergot action on the cock's comb. He must have worked with old samples, since the author obtained the typical darkening from several different samples. However, the action is quite weak, and the drug does not deserve much attention unless it should be possible to isolate the principles in more active form. It possesses resins, such as form the active principles of ergot.

Gossypii Cortex (U. S. P.).—The root-bark of *Gossypium herbaceum* and other species, Malvaceæ. Another ecbolic for which we are indebted to the negroes. It contains several resins. The reports of clinicians and experimenters are not favorable. *Dose:* 2 Gm. = 30 grs. (U. S. P.), commonly used as the * *Fluidextract* or infusion.

VIII. ECBOLICS (OXYTOCICS) AND EMMENAGOGUES.

Ecbolics are remedies which stimulate the gravid uterus to the expulsion of the fetus. When used in the non-gravid condition, they increase the menstrual flow, and are then called *Emmenagogues.* Besides the Ergot group, one may count here:

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* Not official.

Study Materia Medica Lesson 39.

I. All drugs which produce congestion of the abdominal organs. This always extends to the pelvic organs as well.

1. All *Drastic Purgatives.*— Aloes, Myrrh, etc.

2. *Irritant Volatile Oils,* especially Savin, Thyme, Pennyroyal, and Turpentine.

3. All other *Intestinal Irritants:* Cantharides, Quinin, Digitalis, Metals, etc. A similar action is also claimed for Borax, but may be considered doubtful.

It must be remembered that these irritants produce their ecbolic effect only secondarily to a gastro-enteritis. The latter may be so violent as to be fatal without accomplishing the desired result. They should not be employed for ecbolics, but at most as emmenagogues.

4. Application of heat or counterirritants to pelvic region or feet: hot foot- or hip-baths, mustard plasters, hot irrigations of the vagina, etc. These milder measures are only emmenagogue. When nutrition is low, they may be greatly aided by *tonics.*

II. All drugs which stimulate unstriped muscle — Muscarin, Nicotin, Pilocarpin, Physostigmin, Hydrastis, etc.— may act as ecbolics, but cannot be used in practice.

IX. UTERINE SEDATIVES.

In contradistinction to the ecbolics, **Viburnum prunifolium** is employed to lessen the uterine flow, and to quiet the movements of the uterus. It is prescribed in menorrhagia, dysmenorrhea, habitual or threatened abortion, hysteria, etc. There is no experimental foundation for its use. It contains considerable tannin, and is therefore astringent (used in diarrhea and dysentery, and as gargle in pharyngitis, etc.). Large doses are said to paralyze the central nervous system and the heart. *Vibernum opulus* is also astringent, and is recommended in colic and muscular cramps ("cramp-bark").

Viburnum Prunifolium (U. S. P.).— *Black Haw.* The bark. Alkaloid, resins (viburnin); valerianic and tannic acid, etc. *Fluidextract* (U. S. P.), 2 to 5 c. c. (½ to 1 drachm), best with aromatics. (2 c. c. = 30 ♏., U. S. P.).

Viburnum Opulus (U. S. P.).— *Cramp Bark.* The bark. Tannin, etc. *Fluidextract* (U. S. P.), 2 to 5 c. c. (½ to 1 drachm) (2 c. c. = 30 ♏., U. S. P.).

X. REMEDIES USED TO CONTROL HEMORRHAGE.

The measures used to check bleeding (hemostatics) may be divided into those which act locally (*styptics*) and those which affect the body at large (*general hemostatics*).

The principal **local remedies** are those which close the vessels by compression (or suture), cold, suprarenal alkaloid; those which favor clotting (absorbent cotton, pengawahr djambi: the popularly used cobweb is efficient, but septic); and those which precipitate the blood, *i. e.,* astringents, tannin, iron (chlorid or Monsell's solution), alum, vinegar, etc. The wound should be well cleaned before the local styptics are applied.

General hemostatics may be divided into those which lower the general blood-pressure; those which cause vasoconstriction limited to the bleeding area; and those which increase the coagulability of the blood.

Measures Lessening the General Blood-Pressure.— These are useful in practically every case of bleeding (except when the blood-pressure has already been lowered to a dangerous degree by a very profuse hemorrhage. This demands the injection of warm normal saline solution.)

The first desideratum is *rest,* since all movement tends to raise the blood-pressure, and furthermore, to dislodge the clots. Morphin, bromids, and alcohol and other hypnotics may be given to keep the patient quiet. All measures which produce sudden movements (emetics, purgatives, etc.) are contraindicated. The patient should be placed in a *position* which will lower the blood-pressure in the bleeding part as much as possible. *Cardiac depressants* (aconite) are also indicated in every case.

The use of **vasodilating and constricting drugs** gives very uncertain results. It will be easily appreciated that, in order to be useful in hemorrhage, a vasodilator must dilate the vessels of the general circulation, but *not* at the bleeding point. Per contra, a vasoconstrictor must constrict them at the bleeding point, but not elsewhere; in the latter case, the rise in general blood-pressure might easily overcome the local constriction and make the bleeding more free.

General vasodilators (nitrites) are indicated when the hemorrhage is situated in areas which are not easily dilated, *i. e.,* the lungs and muscles. They are contraindicated in bleeding from the brain or splanchnic area.

It is doubtful whether **general vasoconstrictors** are ever indicated in hemorrhage; for their action cannot be confined to the bleeding vessels. The only established exception to this statement is the effect of ergot in post-partum hemorrhage (but as we have stated, ergot is often used against bleeding in other regions).

Specific Coagulants.—An increase of the coagulability of blood is desirable when there is a tendency to excessive bleeding on slight provocation — in hemophilia, purpura hemorrhagica, epistaxis, hemoptysis, excessive menstruation, renal or intestinal hemorrhages, etc. The measures which are claimed to be effective in these conditions are also recommended in aneurism (although they are said to favor embolism).

The principal remedies which are used for this purpose are *calcium chlorid,* and *gelatin.* Most observers attribute the action of the latter to the calcium which it contains, stating that gelatin freed from calcium is ineffective (Gley and Richaud, 1903). The evidence that these drugs accomplish the desired results is not conclusive, although the majority of the clinical observations are favorable. It is well known that the presence of a certain amount of calcium is necessary to the coagulation of blood; but it has never been shown that this calcium is deficient in the diseases named above, for neither gelatin nor calcium hastens the coagulation when added to the blood. However, Dastre and Floresco (1897) claim that the time required for the coagulation is shortened, when gelatin is given systemically; this is confirmed by other observers, and also in regard to calcium. On the other hand, some investigators deny this action; Sackar (1901) refers the effect to intra-vitam agglutination of the corpuscles, producing intravascular precipitation, which would entail the clotting.

It will be seen that there is no rational explanation of the effect of these drugs, if indeed they produce any action. Since they can do no harm, when properly used, they may at least be given a trial.

The **calcium chlorid** is generally given by mouth, to 3 Gm. per day, continued as long as necessary; or it may be injected hypodermically, in 1 to 5% solution. In urgent cases of hemophilia, 100 c. c. of a 10% solution may be injected *very slowly* into a vein, and repeated in twelve hours. Boas (1904) recommends 20 c. c. of 10% solution as enema (after defecation) in bleeding hemorrhoids. The **gelatin** was originally used subcutaneously (100 to 200 c. c. of sterile 1 to 5% solution, injected slowly into the thigh, ***not*** near the aneurism, every 10 to 15 days, until ten to twenty injections have been given.) The treatment is quite painful, and may raise the temperature to 103° F. Tetanus has been a not uncommon sequence, when the solutions were not thoroughly sterilized. Wood (1902) claims that the gelatin is just as effective, only somewhat slower, when given by mouth, and recommends eating three or four ounces of flavored 10% jelly, three times a day.

(Ordinary styptics are generally useless in hemophilia. The inhalation of oxygen has been recommended, empirically. The intravenous injection of ***nucleoproteids*** causes intravascular clotting, but this is promptly fatal, and cannot be utilized therapeutically).

XI. DRUGS WHICH LESSEN THE COAGULABILITY OF THE BLOOD.

In laboratory experiments, the coagulability of blood can be easily diminished or abolished. Leech extract has this effect, whether it is injected, or added to shed blood; albumoses, only when injected; citrates, oxalates, fluorids, concentrated solutions of other salts, formaldehyd, hydrocyanic acid, etc., only on shed blood (by removing the calcium or inhibiting the filbrin ferments). None of these drugs can be used effectively on patients, except by local application. Nevertheless, sodium citrate is sometimes used to prevent threatening thrombosis. It is difficult to understand how it can have any effect whatever.

Hirudo — Leech.

(B) SAPOTOXIN GROUP.

I. PROPERTIES, OCCURRENCE, SUMMARY OF ACTIONS.

The members of this group, the sapotoxins and saponins, are characterized by forming an excessive and persistent foam when even very dilute (1 : 10,000) watery solutions are shaken; by emulsifying fats and suspending fine powders; by dissolving red blood corpuscles and other cells, even in isotonic solutions; and by a general toxicity to all cells. The degree of this toxicity varies greatly in the different members of the series; the more toxic being termed *sapotoxins;* the less toxic, *saponins.*

Chemically, these substances are non-nitrogenous, glucosidal, neutral principles. Many have the ultimate composition $CnH_{2}n - {}_{8}O_{10}$. When heated with dilute mineral acids, they are decomposed into glucose and a ***sapogenin.*** They are generally not attacked by animal ferments. Physically, they possess the characters of colloids: They do not dialyze; they are soluble in water, and are not precipitated by moderate amounts of alcohol; but they do not dissolve in pure alcohol or in fat-solvents. Many are precipitated by saturation with neutral salts, especially ammonium sulphate; by basic lead acetate; etc.

These principles are very widely distributed through the vegetable kingdom, occurring in at least 150 plants, belonging to thirty different families. They are probably formed in the leaves, but are found in all parts of the plants. The foaming is so conspicuous that many of these drugs have received characteristic popular names, soap-bark, soap-root, etc. They are employed, even by non-civilized peoples, for cleaning; and on account of their high toxicity to fish, as fish-poisons.

Their very powerful action on fish is explained by their rapid absorption through the gills. The greater number are scarcely toxic to mammals, as they are not readily absorbed from the alimentary canal. Their local action on the latter, however, results in nausea and vomiting. This constitutes their therapeutic use. Agrostemma, the common corn cockle, is the most dangerous drug of the group, since it is absorbed exceptionally well. Quillaja (soap-bark) may also prove toxic.

II. DETAILS OF ACTION.

Locally, they exert a very marked *irritant action* on the *mucous membranes.* They have an *acrid taste* and provoke a flow of saliva (sialogogue action); if inhaled, they cause *sneezing;* if injected hypodermically, they cause *subcutaneous inflammation.* When added to defibrinated blood, they will *dissolve the corpuscles* and liberate the hemoglobin and the salts — the latter even when the corpuscles have been laked, or fixed by formaldehyd.

If they are **injected directly into the blood,** the most marked symptoms fall upon the *central nervous system,* and are rapidly fatal. At first there are violent *convulsions;* then *paralysis,* especially of the respiratory center. The effect on fish is also paralytic.

Smaller doses given by the blood cause especially *intestinal symptoms,* and death after several days by collapse. Why the symptoms are so largely intestinal is unexplained. Given subcutaneously, they produce these same symptoms, only, of course, much more slowly. If they are applied directly to skeletal or cardiac *muscle* or to nerve-trunks, these lose their irritability at once, and if the solution is fairly strong (1%), there is rigor.

The same train of phenomena of general poisoning is obtained if these poisons are **absorbed from the stomach:** either directly, as in the case of agrostemma, or with the others after the local action has produced a corrosion of the mucous membrane. If the dose is too small for this, only the local effects are observed. These lead to symptoms of gastro-enteritis, vomiting, persistent diarrhea, etc.

III. MANNER OF ACTION.

The toxic action of the sapotoxins and solanin on the **red blood corpuscles**[1] is due to their dissolving the cholesterin contained in the envelope. And there is every reason to believe that this holds also for other tissues. Cholesterin (and indeed any fat, such as cotton-seed oil) is a perfect antidote to the hemolytic action, although it is not so effectual against the central action. The mechanism of this action has been greatly elucidated by the work of G. N. Stewart ('99 to '02). It must be conceived somewhat as follows: The electrical resistance of intact cells is always greater than that of the fluids in which they are bathed, or than that of their own contents. This means that they have an envelope which is partly or entirely impermeable to ions. This impermeability is due to the presence of cholesterin, lecithin, and similar fatty substances, which, on account of their insolubility in saline fluids, interpose a physical barrier to the penetration of most salts, whilst they permit the entrance of fat-soluble substances. Sapotoxins have the property of dissolving these fats, thereby breaking down the barrier, and allowing the entrance of foreign salts and the exit of the contained salts. This disturbance in the salt content of the cell results in its disintegration. If the sapotoxins are saturated with cholesterin or oil before they come into contact with the cells, they are naturally deprived of their activity (Ransom, Hédon, 1901). Serum is also antitoxic through its lipoids. The lecithin-saponin compound, however, is also toxic. Some degree of immunity can be secured through repeated injections.

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[1] Exercise 22.

The central actions of sapotoxins are not as a rule due to the hemolysis, but to a direct action on the brain cells; these are paralyzed by smaller doses than are required for laking.

IV. THERAPEUTICS.

The toxic actions on the central nervous system do not at all come into play, since there is no absorption. Only the *irritant action on the alimentary canal* needs to be considered. This bears a close resemblance to the local action of ipecac, and the therapeutic indications are the same. As *nauseants* and *emetics* they possess the advantage over ipecac that they are not at all absorbed, provided they are given in moderate doses; they therefore avoid the central action of emetin.

The property of emulsifying determines their use as *detergents* in the arts, for the cleansing of articles which are injured by alkalies.

The use of quillaja as an emulsifier for medicinal preparations is not admissible; but some of the less toxic saponins may be used for this purpose (Kobert, 1904).

A certain number of these drugs have some importance or account of stock-poisoning (Vaccaria, Raw Potatoes); others have been used as fish-poisons, as soap and as counterirritants, etc., by the aborigines.

Sarsaparilla, which owes its activity entirely to the sapotoxin or saponin which it contains, formerly enjoyed considerable reputation as an *alterative.* This is no longer accepted at the present time, and if it possesses any action at all it is simply that of a very mild nauseant and cathartic.

V. MATERIA MEDICA OF SAPONIN GROUP.

Quillaja (U. S. P.) [**Quillajæ Cortex,** B. P.].—*Soap-bark.* The inner bark of *Quillaja Saponaria,* Rosaceæ; Chili and Peru.

Fluidextractum Quillajæ (U. S. P.).—One-half alcohol. *Dose:* 0.2 c.c. = 3 ♏. (U. S. P.).

Tinctura Quillajæ (U. S. P.).—One-third alcohol, 20%. *Dose:* 1 c.c. = 15 ♏.

* **Saponaria officinalis.**— *Soap-wort.*— The root or leaves of *Saponaria officinalis,* Caryophyllaceæ; temperate zone. *Dose:* 2.0 to 4.0 Gm.

Senega (U. S. P.) [**Senegæ Radix,** B. P.].— The root of *Polygala Senega,* Polygalaceæ; North America.

Fluidextractum Senegæ (U. S. P.).— Alkaline, three-fourths alcohol. *Dose:* 0.5 to 1.0 c. c. (10 to 15 minims) (1 c. c. = 15 ♏., U. S. P.).

Liquor Senegæ Concentratus (B. P.).— 50% alcohol. *Dose:* 2 to 4 c. c. (½ to 1 drachm).

Syrupus Senegæ (U. S. P.).— 20%. *Dose:* 4 to 8 c. c. (1 to 2 drachms) (4 c. c. = 1 ʒ., U. S. .P.).

Infusum Senegæ (B. P.).— 5%. *Dose:* 15 to 30 c. c. (½ to 1 oz.).

Tinctura Senegæ (B. P.).— 20%. Two-thirds alcohol. *Dose:* 2 to 4 c. c. (½ to 1 drachm).

* **Caulophyllum.**— *Blue Cohosh.*— The rhizome and roots of *Caulophyllum thalictroides,* Berberidaceæ; North America. Also contains tannin and an alkaloid and resins, about whose action very little is known. *Dose:* 0.3 to 2.0 Gm. (5 to 30 grains).

Sarsaparilla (U. S. P.).— The root of *Smilax officinalis* and some other species, Liliaceæ; tropical America.

U. S. P. Preparations:

Fluidextractum Sarsaparillæ.— One-third alcohol. *Dose:* 2.0 to 4.0 c. c. (½ to 1 drachm) (2 c. c. = 30 ♏., U. S. P.).

Fluidextractum Sarsap. Compositum (U. S. P.).— Sarsaparilla, Glycyrrhiza, Sassafras, Mezereum, Glycerin, Diluted Alcohol. *Dose:* 2 c. c. = 30 ♏. (U. S. P.).

Syrupus Sarsap. Compositus (U. S. P.).— Fluidext. Sarsaparilla, Glycyrrhiza, Senna; Oil Sassafras, Anise and Gaultheria. Pleasant, slightly laxative vehicle, especially for iodids. *Dose:* 15 to 30 c. c. (4 to 8 ʒ.) (16 c. c. = 4 ʒ., U. S. P.).

Sarsæ Radix (B. P.).— *Jamaica Sarsaparilla.*— The root of *Smilax ornata,* Liliaceæ; Costa Rica.

Liquor Sarsæ Compositus Concentratus (B. P.).— Contains Sarsaparilla, Sassafras, Guaiac, Licorice, Mezereum. *Dose:* 8 to 30 c. c. (¼ to 1 oz.).

Extractum Sarsæ Liquidum (B. P.).— *Dose:* 4 to 15 c. c. (1 to 4 drachms).

Hemidesmi Radix (B. P.).— The root of *Hemidesmus indicus,* Asclepidaceæ.

Syrupus Hemidesmi (B. P.).— *Dose:* 2 to 4 c. c. (½ to 1 drachm).

II. SOLANIN.

The glucosidal alkaloids, solanin, solanein, and solanidin, which occur in plants of the potato-genus (Solanum nigrum, dulcamara, tuberosum (Potato), Carolinense, and Tomato), possess a typical sapotoxin action. In certain species, particularly in S. dulcamara, they are associated with a small quantity of atropin-like alkaloid and with a saponin (dulcamarin). The latter plant is sometimes used as a nauseant. Solanin has the formula $C_{52}H_{93}NO_{18}$; solanidin, $C_{40}H_{61}NO_2$.

* **Solanum Dulcamara.**— Bittersweet.— The young branches are used. *Dose:* 4 c. c. of the fluidextract.

* *Solanum Tuberosum.*— The toxic principles are distributed throughout the plant, but only very small quantities are found in the pulp of the tuber — too small to produce any action. The quantity is larger in the skin, and especially in very young and in sprouting potatoes, which have sometimes given rise to poisoning.

* *Solanum Carolinense.*— The berries have been recommended in

* Not official.

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epilepsy. They are always given with bromids, and the therapeutic effects of the mixture are probably due entirely to the latter. *Dose:* 4 c. c. of the fluidextract.

(C) SUMMARY OF THE TREATMENT OF COUGH.

I. PATHOLOGIC CONDITION.

The act of coughing may be defined as a coordinated reflex involving the respiratory center, and resulting in the sudden and violent expulsion of air from the lungs. It has a physiologic function in the removal of irritant substances or of accumulation of mucus from the respiratory passages. Like other reflexes, however, it tends to persist after its cause has ceased to be active; or it may become excessive. In either case it will require treatment. It must be borne in mind that cough is merely a symptom, and whilst it may be treated directly, as such; no treatment can be of permanent benefit unless it is also directed against the original cause, if this is still in operation. This cause lies most commonly in the respiratory passages, but there appear to be other conditions which may give rise to cough, or which at least may help in its production. The changes produced in the general circulation by drugs like *digitalis, strychnin,* or the *nitrites* are frequently beneficial. When signs of disease are present in other organs (dyspepsia, etc.), these should receive direct treatment. General measures, such as laxatives, diaphoretics, antipyretics, analgesics, etc., must be used as the indications arise. Removal to a more suitable climate is always advisable, and sometimes necessary in chronic bronchitis. A dry climate is chosen if the secretion is profuse, and vice versa.

II. REMEDIES AFFECTING COUGH.

Since coughing is a reflex act, it may be affected either centrally or peripherally.

(A) For the **central treatment** any drug may be used which depresses the respiratory center. The most useful are the members of the *Morphin Group,* and particularly *Heroin* (see p. 185). Chloroform and bromids are also useful, but their action cannot be limited so nicely to the respiratory center.

(B) The **peripheral treatment** is to be directed against the inflammation and its attendant phenomena. It must be modified according to whether the seat of the inflammation is or is not accessible to local medication. The cause of the inflammation is usually bacterial, and requires *antiseptics.* If seated above the larynx, these may be administered by way of gargles. If below the larynx, inhalations of the volatile antiseptics (Creosote, Turpentine, etc.) are most effective. It is often attempted to secure this object by giving volatile antiseptics by the stomach, on the theory that they are excreted in sufficient concentration by the lung. This may be considered doubtful. However, all the members of the turpentine group, when present in the blood, tend to lessen even aseptic inflammatory processes.

The *sensory irritation,* which is the immediate cause of the cough, may be diminished by demulcents or anodynes. Whilst it is only possible to apply these local measures above the larynx, yet they seem to be beneficial even in more distant irritation. It may be that the solutions spread downward over the surface of the mucous membrane.

Demulcents are colloid (gummy) substances, which appear to act simply mechanically, by excluding the air and bacteria. They play the same rôle to mucous membranes as salves do to the skin (see Chap. XXXI, A). The most important in this connection are *Acacia, Sugar, Licorice,* and the various demulcent teas. *Hot drinks* of all kinds are useful.

Local anodynes act by depressing the sensory endings. They possess in this way no advantage over the central depressants, and are more difficult to apply. *Cocain* and *Atropin* may be used, the latter also in the form of the smoke from burning stramonium leaves, as for asthma. *Hydrocyanic acid* (commonly employed in the form of Syrup of Wild Cherry) also appears to act as anodyne. The most useful anodyne measure, however, consists in the inhalation of steam.

The inflammatory *congestion* may be influenced indirectly by counterirritation or compresses; or directly by local astringents, *Tannin, Alum,* or *Ferric Chlorid* being the most useful.

Next to the cough itself, the most conspicuous symptom of these inflammations lies in alterations of the quantity or character of the bronchial mucus. Remedies which influence this secretion are called **Expectorants.** Their employment becomes particularly important if the inflammation is seated in the bronchial divisions.

The expectorants may be divided into those which diminish the secretion of mucus, being used when this is excessive; and those which increase, and therefore liquefy, mucus, being employed in cases of "dry" cough, in which the irritation arises from thick, scanty, adherent mucus. The expectorants are also divided into *depressant, stimulant,* and *indifferent,* according to their effect upon the general condition of the patient. (Note that these terms do ***not*** refer to their effect upon the mucus!)

Expectorants which increase secretion:

Depressant: Nauseants: Ipecacuanha.
Apomorphin.
Tartar Emetic.
Sapotoxins (Senega).
Indifferent: Neutral Salts (Iodids).
Carbonates.
Pilocarpin.
Stimulant: Ammonia Salts (Carbonate or Chlorid).
Digitalis and Squills.

Expectorants which diminish secretion:

Atropin; Acids (hydrochloric); Turpentine, Terpen hydrate, Essential oils (cubebs); Aromatic Products (Benzoates, Balsams, Creosote, Tar, etc.).

When the accumulation of mucus is very great, it becomes necessary to effect its removal by the employment of emetics.

III. TREATMENT OF COUGH.

The underlying conditions, when known, should receive first consideration, but the symptoms may be treated at the same time. Antiseptics and demulcents are always indicated. Anodynes, central or peripheral, are only to be used when the secretion is not excessive. The choice of expectorants must be governed by the condition of the mucus, and by the general condition of the patient: the depressants are often useful if the cough is accompanied by acute fever. Their depressant action may also be abolished by combining them with strychnin, digitalis, or ammonium acetate.

It will be seen that different cases, and even the same case in its different stages, require very different treatment. The routine treatment of every case by a standard "cough-syrup" cannot be too strongly condemned. However, these compounds have a use in properly selected cases, and we therefore append a list of the most popular formulas.

IV. MATERIA MEDICA OF COMPOUND COUGH MIXTURES.

Misturæ Glycyrrhizæ Composita (U. S. P.).—*Brown Mixture.*—The *dose,* 4 c. c. (teaspoonful) contains: Glycyrrhiza, Sugar, Acacia; Vinum Antimonii, 0.25; Tr. Opii Camphor, 0.5 c. c.; Sp. Æther. Nit., 0.12 c. c.

Syrupus Scillæ Compositus (U. S. P.).—*Hive Syrup.*—*Dose:* 0.5 to 2 c. c. (7 to 30 minims) (2 c. c. = 30 ♏., U. S. P.). 1 c. c. contains Squills, Senega, and 0.002 Tartar Emetic.

Trochisci Cubebæ (U. S. P.).—Cubeb (0.02 Gm. of oleoresin), Licorice, Sassafras, Tolu, Acacia. *Dose:* One every half hour.

Elixir Picis Compositum, N. F.—Wild Cherry, Tar, Tolu, Methyl Alcohol, *Morphin,* and Wine. The *dose,* 4 c. c. (teaspoonful), contains $^1/_{30}$ grain Morphin Sulphate.

Species Pectorales, N. F.—Althæa, Coltsfoot, Glycyrrhiza, Anise, Mullein, and Orris. Used as *infusion* 1 : 10 ad libitum.

Syrupus Pini Strobi Compositus, White Pine Expectorant, N. F.—White Pine Bark, Wild Cherry, Spikenard, Gilead, Sanguinaria, Sassafras, Morphin, Chloroform. The *dose* (4 c. c. = teaspoonful) contains 0.002 Gm. ($^1/_{30}$ grain) Morphin Sulphate.

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CHAPTER XXIV.

OSMOTIC ACTION; CATHARTIC SALTS; DIURETICS.

(A) OSMOTIC (SALT) ACTION.

Introductory.[1]—The strictly chemic changes produced by poisons are a property of their chemic composition, and are therefor specific; differing in kind as well as in degree for each poison. The functional changes resulting from the solution of lipoids, although they are physical, are also confined to a limited number of poisons (the alcohol group and sapotoxins). Another large class of pharmacologic phenomena, however, result from the physical properties of molecules, the so-called "**colligative properties,**" which are common to all substances in solution, and which are entirely independent of their chemic composition. These colligative properties may be measured by physical methods, as will be explained later: by the osmotic pressure, the lowering of the freezing point, and the raising of the boiling point of the solution. The phenomena, to which they give rise in the cell, consist mainly in alterations of the water and salt-content, and of the internal pressure. These result in functional disturbances. *The effects,* as has been said, *may be produced indifferently by any dissolved substance, and are strictly proportional to the number of molecules contained in the unit-volume of the solvent.*

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[1] The student is advised to read the chapter on the molecular physics of gases and solutions in some work of physics, before studying this subject.

The importance of these actions is, however, very different for different drugs. In the muscle-nerve poisons, *e. g.,* the specific actions are relatively so much more intense, that the physical actions are entirely overshadowed and negligeable. In other cases, as with proteids and colloids in general, the molecules are so large that even saturated solutions contain only a relatively small proportion, and therefore cannot exhibit these properties in a marked degree. On the other hand, the physical actions are very conspicuous and important in the case of the neutral salts of alkalies, and they are therefore commonly called "**Salt-Actions.**" In using this convenient term, it must always be remembered that the same actions are produced by substances which are not salts in the chemical sense: by acids, alkalies, alcohols, sugars, glycerin, urea, etc., etc. *Osmotic Action* is therefore a better term.

I. COLLOIDS AND CRYSTALLOIDS.

Graham in 1861 divided soluble substances into two large classes, the colloids and crystalloids. This division has been found so convenient that it has been retained, although it is by no means a sharp one, and it has been found necessary to modify his definitions considerably.

The Colloids have a peculiar physiologic importance since they are the most abundant constituents of protoplasm, and determine its physical characters and many of its chemic properties. All colloids, when in solution, consist of extremely large molecules or rather of collections or "aggregates" of molecules. These aggregates are often 1,000 to 10,000 times as large as ordinary molecules; but each aggregate behaves just like a single molecule. It must be evident that the colloidal solutions possess the colligative properties in only a very slight degree. Furthermore, these large aggregates behave in many ways like fine *solid* particles in suspension: They tend to coalesce and to form precipitates; they can be partly separated from their solutions by passing the latter through appropriate filters; they diffuse but slowly through water, and scarcely at all through other colloids or through animal membranes; they develop only a very small osmotic pressure, and they may be charged with either positive or negative electricity, and therefor wander with or against the electric current.

The quasi-solid character of the aggregate "particles" causes them to exert a great *surface action,* which is very important to protoplasm. In virtue of this, they produce "**adsorption,**" *i. e.,* a condensation of other dissolved molecules on their surface.[1] These condensed molecules are endowed with greater chemic activity, so that colloids may act as catalyzing agents or ferments.[2] They also adsorp water in a similar manner. This "**imbibition**" causes a swelling of the colloids if they are in a solid or gelatinous condition (see below). The adsorption is perhaps an electric phenomenon.

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[1] This power of condensation has long been known in the case of charcoal, spongy platinum, etc. Even relatively coarse particles, such as sand or filter-paper, seem to possess a similar action, though in a less degree; for it has been shown by True & Oglevee (1904) that the toxic action of dilute solutions of metals is diminished if these are treated with sand or other indifferent insoluble powders, which act apparently by removing the metallic salt from the solutions by adsorption.

The manifold resemblances of colloid solutions to suspensions suggest that the aggregates are in reality solid. There can be little doubt that this is true for some, for instance for the colloid metals; but the crystallization of proteids proves as conclusively that the latter form true solutions. It would seem, therefor, that colloids may present all gradations from the solid to the dissolved state, according to the size of the aggregates. *This is not constant,* even for a given colloid, but varies according to several conditions. This fact is of very great importance, for *the size of the colloidal particles determines the fluidity and solidity, or the viscidity, of the solution; the viscidity increasing with the size of the aggregates.* This determines the **three states in which colloids may exist:**

If the size of the aggregates is comparatively small, the solution exhibits the ordinary characters of a fluid; this condition is called a "*sol*" (if the solvent is water, a "hydrosol"). As the size of the aggregate increases, the sol becomes more and more viscid, until it finally sets into a jelly, when it is called a "*gel*" (hydrogel). The gel resembles a solid in preserving its form, when it is not subjected to external agencies. But it also resembles fluids in being readily changed by external causes, and in permitting the penetration of water, and the diffusion of crystalloids. The latter penetrate it almost as rapidly as they would water. Chemical reactions may occur in its interior very much as they would in water. Other colloids, however, cannot diffuse through a gel.

Protoplasm is a gel, of various degrees of fluidity. Dried colloids may be considered as very solid gels. If the size of the aggregates increases still further they are *precipitated, i. e.,* they lose all the characters of solutions, and become typical solids. The question will naturally suggest itself: **What determines the size of the aggregates?** It is a familiar phenomenon (*f. i.,* in the case of oil or mercury) that small particles suspended in a liquid tend to coalesce to form larger particles. The molecular particles in colloid solutions possess the same tendency, as is shown by the readiness with which they may be precipitated. They are only kept apart by their molecular motion, and by their electric charges. The more the motion is increased (*e. g., by increasing the quantity of solvent, or by raising the temperature* within the limits which do not produce chemic changes) the greater will be the tendency of the aggregates to fly apart, and to form smaller aggregates. It is quite conceivable that this motion and separation are really *electric phenomena.* We know that the colloid particles may be charged with electricity, either positive or negative. Since all the particles in a solution are charged with electricity of the same sign (let us say with negative electricity, since this is the case with most protoplasm), they repel each other, just as do the gold leaves of an electroscope. Any increase of the charge (negative in our example) increases this repulsion, and consequently diminishes the size of the aggregates and the viscidity of the solution. If, on the other hand, a small amount of electricity of the opposite sign (positive) is introduced, some of the charges carried by the particles are neutralized and they tend to coalesce. If this (positive) electricity is increased beyond the point when all the original (negative) charges are neutralized, the particles will become charged with positive electricity, and again fly apart. These modifications may be produced by the passage of an electric current; and also, by the electric charges of the ions (see next chapter) of electrolytes. The latter (salts, acids, and bases) may therefor influence the state of aggregation of colloids by withdrawing water and by altering the electric charges. There is yet another way in which the state of aggregation may be varied, viz., by *chemic action.* This introduces at once profound changes in the state of aggregation, and in the electric condition.

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[2] Colloid metals, i. e., metals in colloid solution, acquire such catalyzing properties.

All these changes which we have just described for colloid solutions may be observed in *living cells:* Withdrawal of water, lowering of temperature, decrease of the electric charge, and certain chemic changes, render the protoplasm more viscid, opaque, and granular, and diminish its motility. A reversal of these conditions leads to the opposite effects.

Crystalloids[1] possess relatively small molecules, possess the colligative properties in a high degree (*e. g.*, they can exert a large osmotic pressure) and diffuse readily through animal membranes and through colloids generally. They do not form aggregates or gels, and do not exert the surface actions. They are divisible into electrolytes and non-electrolytes (see next chapter).

II. OSMOSIS.[2]

This term is applied to the physical phenomena which result when solutions are brought in contact through membranes permeable to the solvent. It covers the subjects of diffusion and dialysis.

1. Hydrodiffusion.— If a solution of common salt be poured into a vessel, and on this some water, it will be found that, even if every conceivable precaution has been taken not to mix the liquids, the upper watery layer will after a time contain sodium chlorid molecules, and finally the composition of all layers of the liquid will be uniform.

This is explained by the fact that the salt molecules are constantly in motion, traveling freely in all directions in the liquid, in the same manner as gas molecules. A certain number will always pass toward and into the watery layer, and remain there. Other molecules will return from the upper to the lower layer. But more will go in the first direction than in the second, until the proportion of molecules in all layers of the liquid is the same. Whilst the process is infinitely more slow than in the case of gases, the final outcome is precisely the same.

2. Permeable Membranes.— Let us suppose that we separate the two liquids by a membrane, instead of placing them in direct contact. If the molecules of both salt and water pass readily through the physical pores of this membrane, the phenomena of hydrodiffusion will not be changed in any essential feature.

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[1] The classification is not determined by the formation of crystals, but by the characters given in the text.

[2] Exercise 23.

The process of diffusion would, of course, be somewhat slower, for a certain number of molecules would not hit upon a pore, and would rebound.

A "permeable membrane," then, slows, but does not otherwise modify, the process of hydrodiffusion.

3. Semipermeable Membranes.— *Osmotic Pressure.*— A "semipermeable membrane"[1] is one which allows the passage of one sort of molecules (usually the solvent), whilst impervious to another (usually the dissolved substance). The interposition of such a membrane between a solution and its solvent introduces very important modifications in the above process, and results in the development of "osmotic pressure."

Every molecule, by striking against the walls of the container, or against other molecules, exerts a certain pressure, which is precisely the same whether the substance is in the form of a gas or of a solution. If the same number of molecules per cubic space exist in two solutions separated by a semi-permeable membrane, the pressure will be equal on each side of the membrane. The nature of the molecules is immaterial in this, as long as they all penetrate through the membrane with equal readiness. If all the molecules can pass through the membrane, an exchange will take place; but since as many pass to one side as to the other, there will be no difference in the pressure in the two compartments. If, on the other hand, the molecules on the one side can pass through readily, whilst some of the molecules on the other side are not capable of diffusing through the membrane, then the pressure in the two compartments will become unequal.

The non-diffusable molecules will all rebound from the membrane, and so remain confined to their own side. The diffusible molecules will, like gases, tend to pass through, irrespective of the other molecules, until they exist in equal concentration on each side. If a solution consisting of x molecules of salt and $(y - x)$ molecules of water per cubic centimeter were inclosed in a closed vessel and separated from water containing y molecules per cubic centimeter by a semi-permeable membrane, then water would pass into the solution until it also contained y molecules of water per cubic centimeter. But it would then also contain x molecules of salt. Its total molecular concentration per cubic centimeter would therefore be $y + x$; higher by x than that of the liquid outside of the vessel. The pressure in the vessel would therefore be increased by x molecules.

This excess of pressure is called the "*Osmotic Pressure,*" or "Osmotic Tension."

The process corresponds exactly to the diffusion of gases; so that it may be said that dissolved molecules behave precisely like gaseous molecules (*Van't Hoff's Theory*).

The osmotic pressure may be measured directly by placing a sugar solution in a porous cup, the walls of which have been coated with a deposit of ferrocyanid of copper. The cup is provided with a manometer, and dipped in a vessel of water. By the direct measurement, it is found that the osmotic pressure exerted by a molecule in solution corresponds quantitatively to the pressure of a molecule in gas form; and ***the osmotic pressure obeys the laws of gases.*** As applied to osmotic pressure, these would read:

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[1] The most typical semipermeable membrane is formed of ferrocyanid of copper.

Boyle-Mariotte's Law: With constant temperature, the osmotic pressure of a solution is proportional to its concentration.

Gay-Lussac's Law: With equal concentration, the osmotic pressure grows by $^1/_{273}$ for each degree C.

Avogadro's Law: With equal osmotic pressure and equal temperature, equal volumes of solutions contain the same number of dissolved molecules, and the same number as would be contained in an equal volume of gas of the same temperature and presence.

The pressure exerted by a ***gram-molecule*** (the molecular weight expressed in grams) or "***mol***" of any substance equals 22.34 atmospheres. In a "molecular" solution therefor (one containing a mol dissolved in a liter of solvent) the osmotic pressure would raise a column of water to a height of about 725 feet! The osmotic pressure of the salts in the blood would raise it about 250 feet. This may suffice to indicate the enormous molecular force latent in solutions.

There exists some confusion in the conception of ***molecular solutions*** (abbreviated as "M"). The definition given, that of Raoult, is undoubtedly the correct one. It is inadmissible to dissolve the mol in water enough to make a liter (Arrhenius's method), as is commonly done in making chemical solutions.

Molecular solutions are sometimes called "normal." This is objectionable; for the ***normal solution of chemists*** differs from the molecular solution, in that the molecular weight is divided by the valence. The ***normal solutions of physiologists*** are again quite different from the above; they are simply saline solutions of a strength of 0.6 to 0.9%.

An actual osmotic pressure will only be developed if the solution is confined; if it is free to expand, the incoming molecules will merely increase the volume of the fluid.

In this way a single molecule of a non-diffusible salt would theoretically be capable of attracting an infinite amount of water across a semi-permeable membrane — for it is evident that the number of H_2O molecules per cubic space would always be less, by the molecules of salt, than they are in pure water.

The rapidity with which water will pass into the salt solution across the same impermeable membrane will, of course, depend upon the concentration of salt; *i. e.*, the partial vacuum of H_2O molecules in the solution. The rate of osmosis will therefore be slowed as the process progresses.

If two solutions having the same molecular concentration in dissolved substance (*i. e.,* which are "*equimolecular*") are separated by a semipermeable membrane impermeable to the dissolved substance, it is evident that no exchange of liquid will occur. Such solutions, having the same osmotic tension, are called "*isotonic*" to each other. (In physiologic literature "isotonic" usually means solutions having the same concentration as blood-serum.)

It is scarcely necessary to mention that equimolecular solutions of different substances do not contain the same percentage of the dissolved salt, but the same number of gram-molecules. The molecular weight of NaCl being 58.4; and of KCl, 74.4 — a 7.44% solution of the latter would be isotonic to a 5.84% solution of the former.

If one solution has a greater molecular concentration than the other, water will pass from the weaker into the stronger solution until both have the same concentration. The stronger is then called "*hyper-isotonic*"; the weaker, "*hypo-isotonic.*" Both, not being isotonic, are called "*an-isotonic.*"

Another class of membranes — and by far the most important from our standpoint, since they are most generally represented in the animal body — are only **partly semipermeable;** *i. e.,* they are partly permeable to salts, though less readily than to water; and they are more permeable for some substances than for others. In this case the results will be intermediate between permeable and semipermeable membranes. They obey at first, for the main part, the laws of the latter; later, of the former. We may study this on several hypothetic examples.

1. Let us assume a membrane *perfectly permeable to water and NaCl, perfectly impermeable to proteids,* and separating solutions of these two substances. It will be plain that if the NaCl passes as readily as water, it will obey precisely the same laws as the latter; in other words, our NaCl solution will behave precisely like water, and this no matter what its concentration. With a membrane of this kind, the weakest proteid solution would in the end be hyperisotonic to the strongest NaCl solution.

So that equimolecular solutions are isotonic only if the separating membrane is equally impermeable to both dissolved substances.

2. Let us assume a membrane which is perfectly permeable to water, and *twice as permeable to NaCl as to sugar; i. e.,* that if solutions of equal concentration of these two substances are diffused across the membrane against pure water, twice as many molecules of NaCl will pass in a given time into the latter than of sugar.[1] Let us assume

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[1] The relative quickness with which different substances in equimolecular solutions pass through a given membrane is called the "*Initial Rate of Osmosis.*"

that this membrane separates equimolecular solutions of these two substances. Then, in a given time, when x molecules of sugar have been passed into the NaCl solution, $2x$ molecules of NaCl will have passed into the sugar solution. A corresponding amount of water will also have passed in order to keep the concentration of the H_2O molecules constant.

So that the less easily diffusible substance produces at first a higher osmotic tension than the more easily diffusible.

It will be readily understood, however, that when the ratio of NaCl molecules has become the same in both solutions, the exchange of sugar molecules will still be proceeding, and will gradually lessen the difference in osmotic tension until both solutions, in the course of time, will again become isotonic.

It is largely by virtue of this different permeability of the cell-wall to different substances that the cells of the body are able to preserve their integrity in the face of considerable changes in their environment.

All cells are relatively impermeable to proteids; their permeability to other substances is, however, very different for the individual tissues. Thus, the intestinal wall is impermeable to sulphates, which pass the kidneys with great readiness.

If a membrane is **impermeable** to both solvent and salts, no osmotic tension can, of course, be developed, since this presupposes the more ready passage of one molecule than of another.

4. Laws of Osmosis.— For convenience, the data which have been discussed in the preceding paragraphs may be summed up in the form of laws:

1. Solutions separated by a membrane permeable to water tend to have an identical molecular composition, both in number and kind of molecules.
2. If the membrane is perfectly permeable to both solvent and dissolved substance, the exchange of molecules will take place without change in pressure or volume.
3. If the membrane is less permeable to the dissolved substance than to the solvent, an increase of liquid, or increase of tension, will occur in the stronger solution.
4. If a membrane is differently permeable to one dissolved substance than to another, equimolecular solutions of the less diffusible substance will be hyperisotonic to the more diffusible.

III. ELECTROLYTIC DISSOCIATION.

Calculation of Osmotic Pressure and Molecular Concentration.—Since it is very difficult to construct perfect semi-permeable membranes, the osmotic pressure is not usually measured directly, but is calculated by diluting the solution until it is isotonic to a known solution in its effects on cells; the laking of red corpuscles being generally taken as the index (Hamburger's method). For the determination of the molecular concentration, advantage is taken of the fact that the *boiling and freezing point* of solutions are proportional to their molecular concentration. The determination of the freezing point, by Beckmann's apparatus, is particularly convenient.

The depression of freezing point (denoted by Δ) is strictly proportional to the molecular concentration; every mol of substance per liter of solution depressing the freezing point of water by 1.85° C., and this no matter what the nature of the substance (*Raoult's Law*).

According to this law, the molecular concentration, and therefore the freezing point, osmotic tension, etc., should be calculable by dividing the per cent. of the solution by $^1/_{10}$ the molecular weight of the dissolved substance. This is found to hold true for concentrated solutions of all substances, and for dilute solutions of *non-electrolytes*—substances which do not conduct the electric current, such as the sugars, urea, glycerin, alcohol, etc. Dilute solutions of *electrolytes*—salts, acids, or bases,—however, show a greater concentration than would be deduced from Raoult's law.

A solution of NaCl containing 0.584 gram of NaCl per liter (equals $^1/_{100}$ mol) should depress the freezing point by 0.0185°. It is found, however, that its depression is nearer to 0.03°; almost twice as great as would be expected. Very dilute solutions of Na_2SO_4 have three times the calculated concentrations; those of H_3PO_4, four times.

To account for these differences, *Arrhenius* advanced the hypothesis that a certain proportion of the electrolytic molecules separate into their constituents: NaCl into Na and Cl; Na_2SO_4 into Na, Na, and SO_4; H_3PO_4 into H, H, H, and PO_4. Each of these fractions exerting the colligative properties of molecules, would cause a corresponding depression of the freezing point. *The proportion of molecules which undergo this dissociation is proportional to the dilution.* We can imagine that, as the molecules separate from each other, their constituent parts also separate.

The degree of dissociation is fairly constant for the same degree of dilution. In 1% solution of NaCl (and in blood) about 82.8% of the molecules undergo this process, and about the same percentage in equimolecular solutions of KCl or NH_4Cl. Dissimilar elements, such as Mg, Ca, SO_4, PO_4, etc., have a different constant. If several salts are present in a solution—particularly if they have a common ion—

the degree of dissociation of each salt will be less than if it were present alone in the same concentration, but greater than if it were present alone in the concentration corresponding to the sum of the several salts.

The total molecular concentration of a dilute solution of a single salt corresponds to the number of undissociated molecules, plus the number of dissociated molecules multiplied by the number of parts into which they divide. For instance, if 80% of the NaCl molecules in a solution are dissociated, the concentration will be $1 - 0.8 + (0.8 \times 2) = 1.6$ times the theoretical; if 80% of Na_2SO_4 is dissociated, it will be $1 - 0.8 + (0.8 \times 3) = 2.6$.

Limitation of Terms.— To avoid confusion it may be well to confine the term "*mol,*" or better, "*molion,*" to the molecular concentration actually deduced from the freezing point (*i. e.,* 1.6 in the preceding example of NaCl); and "*gram-molecule*" to the concentration deduced from the molecular weight (*i. e.,* 1 on the example), without taking account of the dissociation. The abbreviation "M" is always applied to the latter. Several solutions may be related to each other in the following ways: *Equimolecular* (same number of gram-molecules); *Equiosmotic* (same number of molions); and *Isotonic* (same effect on a given cell).

The dissociation of salts, as revealed by the freezing point, bears a striking relation to the conductivity of salt solutions for electricity. It has been found that salt solutions conduct electricity proportionately better the more they are diluted. If, *e. g.,* a solution which contains 0.1 mol has a coefficient of conductivity which we will call "K," a solution which contains only 0.01 mol will have a coefficient higher than $\frac{K}{10}$. This increase is exactly proportional to the increased dissociation, as estimated by the freezing-point method. From this it may be concluded that electricity is conducted only by the dissociated parts. These fractions of the molecules are called **ions.**

Theory of Ionization.— Electricity may be assumed to consist of atom-like elements, "*electrons,*" which are united with the constituents of the salt molecules. According to the theory of the twofold nature of electricity, there are *two kinds of electrons,* positive and negative, which may be denoted as ⊕ and ⊖. The ⊕ is combined with the H, metal, or so-called basic constituents. These are therefor said to carry a positive charge; consequently they wander to the negative pole or cathode, if a current is passed through the solution, and are called *cathions.* The ⊖ combines with the "acid radicle" of a salt, or with the OH of a base, which therefor carry a negative charge, go to the anode, and are called *anions.* In concentrated solutions, the two charges approach sufficiently close to neutralize each other, and the two ions combine into an ordinary molecule, *e. g.,* NaCl. In dilute solutions they are separated so far as to exert no attraction, and act as independent molecules; they might be represented as $\mathrm{Na}\overset{\oplus}{\wedge}$ and $\mathrm{Cl}\overset{\ominus}{\wedge}$, or more briefly, as $\overset{\ominus}{\mathrm{Na}}$ and $\overset{\ominus}{\mathrm{Cl}}$.

[Another hypothesis is finding favor, according to which there is ***but one kind of electron,*** viz., the negative; the positive electron being merely an unsaturated affinity for a charge. The molecule NaCl would therefor be represented as $\mathrm{Na}\overset{\ominus}{\wedge}\mathrm{Cl}$; the ions as Na and $\mathrm{Cl}\overset{\ominus}{\wedge}$. There is no difficulty in stating most of the facts in the terms of either hypothesis, but it is more convenient to retain the terms positive and negative electrons.]

It is scarcely necessary to insist that the ***ions are not identical with atoms*** (from which they differ in that they carry charges), nor with the free elements (which exist as molecules). In a dilute solution of NaCl there does not exist metallic Na ($\mathrm{Na}\overset{\ominus}{\wedge}\mathrm{Na}$) nor gaseous chlorin ($\mathrm{Cl}\overset{\ominus}{\wedge}\mathrm{Cl}$), but Na ions ($\mathrm{Na}^{/}$) and Cl ions ($\mathrm{Cl}\overset{\ominus}{\wedge}$), whose properties are altogether different. It must also be remembered that this ionization exists in only a limited class of compounds, viz., in all acids, bases, and salts (***electrolytes***), and not in compounds which do not conduct electricity (***non-electrolytes***).

The electric charges are especially important, since they may leave the ions to combine with the tissue elements, so that the electrolytes cause electric stimulation of the protoplasm (see Chapter XXV, A).

IV. PHYSIOLOGIC PHENOMENA OF SALT ACTION.

It may now be attempted to apply these physical processes of salt action to the phenomena of life. It is necessary to distinguish between isotonic and *an*isotonic solutions, but it will be seen that salt action always produces much the same final results, although the means by which these are brought about are exactly opposite in the different cases.

1. *Effects on the Composition of the Cells.*—Most cells behave as if they were surrounded by a partly semipermeable membrane. If the molecular constitution of the medium surrounding the cells be in any way changed, this will effect, in the first place, a change in the total water or salt content of the cell. A hyperisotonic solution will cause the withdrawal of water, and a hypoisotonic solution the withdrawal of salts. If the ratio of the different salts in the surrounding medium is not the same as that in the cells, their ratio in the latter will also be altered. Again, when salts are drawn out of the cell, it must be expected that certain of its salts will leave more quickly than others.

The changes will be the greater, on the whole, the more the composition of the surrounding liquid departs from that of the cell. The total molecular concentration of the plasma, lymph, and other body fluids (except urine and gastric juice) of all mammals is very close to 0.33 mol per liter, corresponding to Δ 0.56. The concentration of the protoplasm itself is somewhat higher, since it tends to be constantly increased by the chemical processes of the cell. The normal concentration of the blood and lymph must be considered the best for the function of the cell. Its maintenance is evidently of the highest importance, to judge from the fact that it resists very violent measures. It is not altered by the quantity of fluid or salt in the food; nor by hydremia produced by hemorrhage; nor by thickening the blood by profuse diaphoresis. The intravenous injection of anisotonic solutions alters it but temporarily. About the only method of raising it permanently consists in interfering with the regulating mechanism, by seriously injuring the kidneys; and then it proves fatal when the Δ approaches 0.8° C. The importance of comparatively slight changes in the concentration is also shown strikingly by the red blood corpuscles. These swell in hypoisotonic, and shrink (crenate) in hypertonic solutions. If the serum is diluted to Δ 0.35, the hemoglobin begins to leave the corpuscles, their structure being destroyed.[1] There is reason to believe that the same holds for most other cells, and that the limits between which cells of mammals can functionate at all, are comprised between Δ 0.35 and 0.6 or somewhat higher. This, however, is not the limit of life: In the lower marine animals, the Δ of the blood is much higher, and in the lower sweet-water animals it is much lower. In the former, a concentration equal to that of the serum of mammals, would liberate the hemoglobin. In other words, the resistance of cells is somewhat adapted to their normal environment. This resistance is curiously developed in the small fish Fundulus, which thrives equally well in sea water and in distilled water. It is due, in this case, to a high degree of impermeability to both water and salts. With most cells, however, any departure from the normal concentration of the liquid in which they are bathed, produce the structural changes which we would expect; these can be best seen in monocellular organisms or ova: these show shrinkage or swelling, condensation or liquefaction, precipitation or solution. These often lead to even more important *secondary decompositions,* which may cause the cell to swell even more in a hyperisotonic solution, than they do in water (Sollmann, 1904).

All these changes are referable to alterations in the *total* molecular concentration. The accompanying changes in the ratio of the different salts are of at least equal importance, as will be shown in the next chapter.

The cells have a protective mechanism against these changes, by what may be termed a *selective permeability* of their cell wall; some ions passing in or out of the cell more readily than others. This is so adjusted that a cell will preserve its normal composition in the face of the ordinary accidental changes of its environment; although it is not proof against the greater artificial changes. This selective permeability varies for each class of cells: some being impermeable to one substance, and others to another. It appears also as if the permeability were often greater in one direction than in another. Whilst these functions may be considered to be physical, depending solely on the character of the cell wall; they are nevertheless intimately connected with the normal structure of the cell, and are greatly modified after death.

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[1] Exercise 46.

2. *Effects on the Functions of Cells.*— These physical alterations in the composition of the cells entail corresponding changes in their function, consisting in a mild or strong stimulation, often irritative; passing into depression if the changes have been large. The irritant phase seems to predominate with hyperisotonic solutions, whilst hypoisotonic solutions tend more to depression.

With most cells the main changes fall upon their *metabolism.* These nutritive changes are most pronounced in the cells of lowest vitality. As a rule, pathologic formations possess less resistance than normal tissue, so that one of the most conspicuous phenomena of the general salt action is the breaking-down of pathologic formations, no matter what their origin, and whether they are chemic or anatomic. Other specialized tissue also respond by their proper functions: Abstraction of water from a *nerve or muscle* causes contraction; the unfertilized eggs of certain marine animals undergo parthenogenetic development, etc. (J. Loeb, 1899, 1901).

If a very strong salt solution is injected directly into the circulation, the main symptoms will arise from the **central nervous system.** They consist in stimulation, with subsequent paralysis, being similar to the effects of asphyxia.

3. Effects on the Blood and Lymph.— Fate of Salt Solutions Within the Body.— In what concentration and by whatever channels salts are introduced into the body, they will *tend to increase the quantity of blood,* or rather of plasma; and to render it more watery and less viscid; in other words, to produce *hydremic plethora.* If isotonic or hypoisotonic solutions are introduced, they will dilute the blood by their own fluid; if hypertonic solutions are injected, the blood will draw fluid from the tissues until it has resumed its original concentration. The result will be hydremia in either case. If anisotonic solutions are introduced, they will temporarily alter the molecular concentration of the plasma.

However, *the blood possesses a remarkable power of resuming its normal condition:* its total molecular concentration, ratio of individual constituents, ratio of corpuscles to plasma, and total quantity (in about this order). This process of restitution takes place very rapidly; it is far advanced before a quick intravenous injection can be completed; the molecular concentration returns to very near normal within ten minutes; the quantity of blood and individual constituents are restored somewhat more slowly; but they are almost normal in half an hour; after two hours, the blood presents only very slight abnormalities, even when very large injections have been made (Sollmann, 1901).

The *total molecular concentration* is the first factor to be restored; this is accomplished mainly by the passage of the dissolved molecules: If a *hyperisotonic solution* is injected, the injected molecules leave the blood very rapidly. Other molecules leave more slowly, and water is taken up into the blood. As soon as the normal molecular concentration is restored, the phenomena become identical with those following the injection of isotonic solutions.

If a *hypoisotonic solution* is injected, the principal phenomenon at first is the passage of molecules into the blood, the injected molecules leaving the plasma very slowly. The water also leaves only gradually, *i. e.*, mostly after the normal concentration has been reached; and then by the same process as with isotonic solutions.

If an *isotonic solution* of a single salt (sodium chlorid or sulphate) is injected, both the fluid and the injected molecules leave the circulation; the molecules somewhat more rapidly. At the same time, other molecules enter the circulation. This process continues (for about 2 hours), until the original quantity of blood and its original composition have been practically restored.

It will be seen that the restitution of the blood consists in a process of exchange with the remainder of the body. There can be no doubt that the tissues themselves (especially the muscle-cells; Engels, 1904) play the most important rôle in the rapid exchange which we have so far described. The quantity of material of which the tissues can dispose without visible change is astonishingly great; but very large injections will give rise to ascites, effusions, etc. In addition to the tissues, the lymph and urine flow and all the secretions of the body are also increased; and to them falls the work of finally removing the injected substance from the tissues, out of the body. The tissues act the part of elastic reservoirs, as it were, quickly relieving the blood of the disturbing element, to again give up the abnormal substances as rapidly as they can be removed by the more slowly acting excretory mechanisms.

Physical processes, notably osmosis and filtration, play a very important part in the exchange with the tissues, and in the increased lymph-flow. Indeed, it is scarcely necessary to invoke any vital mechanism for their explanation.

4. Effects on the Urine.[1]— The hydremic plethora results in an increased elimination of urine. The excretion of water and the injected substance is especially increased; the other urinary constituents are generally decreased, as concerns their percentage; although their absolute quantity is usually increased. (The saline diuresis would therefore result in a "flushing of the body.")

The concentration of the urine varies with the concentration of the solution which has been introduced: it may fall as low as Δ 0.12, or rise as high as Δ 3.0° C. On the whole, the composition of the urine approaches the more closely to that of the blood, the faster the diuresis.

The *degree* of diuresis (the total quantity exerted) depends largely on the quantity of solution (both of the dissolved substance and of the water) which has been introduced; but the *rate* of diuresis (the quantity excreted within a short time after injection) depends largely on the concentration of the solution, if this is given intravenously (water, which is so strongly diuretic when taken by mouth, may diminish the urine when injected by a vein).

The diuretic action of saline solutions is largely physical, and can be reproduced point for point in dead kidneys (Sollmann, 1903 to 1905)[2]

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[1] Exercise 65.

[2] Exercise 70.

(except the effect on the composition of the urine). It is explained by the hydremic plethora; the increased glomerular pressure, and the lessened viscidity of the blood. This is aided, in the case of hyperisotonic solutions, by the dehydration and shrinkage of the renal cells. (This explains the statement in the preceding paragraph.) All these processes favor glomerular filtration.

The physical element in the diuresis is especially conspicuous in the early periods of the diuresis, when the changes in the blood are relatively large.

It has been observed, however, that the urinary changes may persist, in a slight degree, after the blood has apparently returned to normal. This suggests the coöperation of a vital stimulation, produced by the (very slightly) altered composition of the blood.

In the **ordinary secretion of urine,** osmosis *appears* to be an obstacle, rather than an aid; for the molecular concentration of urine differs quite widely from that of the blood (Δ urine, ordinarily, 0.9 to 2.1; extremes, 0.12 to 3.0; Δ blood, 0.55 to 0.60); and the kidney has to perform a very considerable labor to overcome the difference in osmotic pressure. However, this work seems to be in no way injurious.

5. The Role of Osmosis in the Absorption of Solutions from Serous Cavities and Lymph-Spaces.— This absorption is almost entirely physical, for it occurs quite well in dead animals, although it is naturally more rapid when the circulation is intact, because the absorbed products are then more rapidly removed. Osmosis plays a very important part in the absorption, especially if the solutions are anisotonic. If a hypoisotonic solution is introduced, osmosis causes the rapid absorption of water; with hyperisotonic solutions, the volume of the fluid will at first increase, until it has become equimolecular with the plasma. At this time, however, the fluid is really hypoisotonic to the non-diffusible constituents of the cells and blood, so that it would be eventually absorbed, by the operation of osmosis alone. (The osmotic absorption is quickened if the body fluids are rendered hyper-osmotic, as by nephrectomy). Ordinarily, however, the osmotic absorption is very slow after the solution has become isomolecular; and other factors intervene to hasten the process. Of these, filtration and imbibition are the most important. The *filtratrion*-pressure is furnished especially by muscular, respiratory, and peristaltic movement. It may be increased by massage.

The term "*imbibition*" is applied to the familiar phenomenon of the swelling of pieces of glue, gelatin, agar, tissues, and other colloid gels, when these are placed into solutions (F. Hofmeister, 1890 and 1891). This process is quite distinct from osmosis, although both may take place side by side. Imbibition is probably analogous to adsorption.

Hamburger has shown that when a solution is placed in a gelatin cylinder, and this is immersed in a circulating current of the same solution, the stagnant fluid in the cylinder passes gradually through the gelatin into the circulating fluid. The phenomenon is obviously analogous to the absorption of isotonic solutions from serous cavities, and helps to explain the latter. Hamburger considers this process an imbibition-effect.

Many physiologists consider that *vital forces* also coöperate in the absorption; the possibility of this cannot be denied; but there is scarcely any positive proof in its support; if it plays any rôle, this must be quite subsidiary.

6. In the **absorption of effusions** or serum from serous cavities, the cooperation of osmosis is almost excluded, for these contain non-diffusible proteid constituents, as well as the tissues. However, the proteids of these fluids tend to break down constantly into more diffusible molecules (as shown by the fact that exudates generally depress the freezing point somewhat more than does the blood). Osmosis therefore plays a part, but this must be relatively small. The existence of proteids also limits the operation of imbibition, for proteids are not imbibed by colloids. This leaves filtration as the main factor in the absorption of proteid-containing fluids. The absorption of these liquids is consequently a much slower process than that of salt solutions.

Effusions of a molecular concentration inferior to that of the blood would be promptly absorbed; or rather, they could not be formed. Since they, like other body fluids, owe their concentration mainly to their content of sodium chlorid, it is evident that a deficiency of this salt in the body will tend to lessen the production of effusions, and hasten their absorption. This is the rational basis of **the treatment of nephritic edemas by withholding salt from the food** (advocated by Widal and Javal, 1903). The treatment is not always entirely successful, for the salt is not generally the cause of the edemas, but only a factor in their production. It is believed, however, that an actual salt retention occurs in some types of nephritis, owing to diminished permeability of the kidney to salts. These would be most favorably affected by salt-withdrawal. In other cases, the effusions are removed more effectively by administering salts, through their diuretic action. Actual trial alone can decide which form of treatment is needed in a given patient.

7. **Absorption from the Alimentary Canal.**— This is probably even more dependent upon forces other than the osmosis than is absorption from serous cavities.

Filtration is very important, but vital action cannot be denied. Thus, it has been shown that in the excised and surviving intestine, immersed in a solution, a passage of fluid takes place from the lumen to the surrounding fluid, even when the two fluids are identical (Cohnheim, 1899). This cannot be explained on any theory as osmotic. It stops much earlier than the muscular contractions, so that it cannot be filtration, and we must be content to call it vital.

Osmosis, however, has some importance in *intestinal absorption.* The time during which the food remains in the alimentary canal is ample to effect osmotic exchanges between the intestinal contents and the blood. An isotonic condition becomes established quite promptly (but is not completed in the stomach, E. Otto, 1905).

This equalization, with the absorbable salts, is always brought about in a way to facilitate absorption: hyperisotonic solution being rendered isotonic rather by the absorption of salt than by the pouring out of fluid; whilst hypoisotonic solutions are rendered isotonic by the absorption of their water. (In other situations than the alimentary canal, the equalization takes place more uniformly in both directions.)

These changes result in corresponding alterations in the composition of the cells of the gastric and intestinal mucosa, which are therefore also subjected to osmotic salt action. This causes irritation. When the irritation is mild, it increases secretion, absorption, and peristalsis. More severe grades of irritation, however, produce emesis and inflammation.

Salts which are not absorbable by the intestine (**cathartic salts**) are reduced to isotonic conditions by the absorption of fluid. This fluid is retained in the intestine with the salts, increasing the bulk and fluidity of the intestinal contents, and serving as a mechanical stimulus to peristalsis. This explains largely the cathartic effects of these salts.

V. ACTIONS OF WATER.

The administration of water, in quantities larger than can be immediately eliminated, leads to a temporary increase of the water content of the fluids and cells of the body; a removal of their salts; and alterations in the proportions of their ions. These changes in turn produce physiologic phenomena, characterized especially by increased secretions, and by changes in metabolism. The effects vary according to whether the quantity of water is normal or excessive; and according to the channel by which it is introduced.

1. Intravenous Injections.—The immediate effects of small amounts, slowly introduced (and especially of *hypodermic injections*) bear a general resemblance to those following the injection of isotonic salt solutions. The changes in metabolism and urine are probably similar to those which occur on taking water by mouth. Larger doses and rapid injection introduce important modifications. Hemoglobin appears in the urine, from the laking of the blood corpuscles. The respiration is slowed and the blood-pressure is lowered. The central nervous system shows rather late paralysis and convulsions. The diuresis is quite small, since the hypoisotonic condition of the blood slows the renal circulation by the swelling of the kidney-cells. The excretion of water occurs mainly by other channels, so that there is usually a serous diarrhea, increased salivation, etc. The fatal dose of water (by intravenous injection) is somewhat smaller than that of normal saline solution; distilled water is again somewhat more toxic than well water.

2. **Distilled Water** is also markedly more poisonous to most lower organisms and to isolated tissues. Even fish die quickly in oxygenated distilled water. This effect is partly due to traces of metallic impurities if the distillation has been conducted in copper stills; and to the presence of ammonium compounds, if these are not removed. But even absolutely pure H_2O is more poisonous than well water. This is due to the fact that the well water, which contains traces of salts, does not remove the salts so thoroughly from the tissues; these salts being necessary for life. *This toxic action cannot occur by the drinking of distilled water by higher animals,* which obtain their salts from food rather than from water: The salts of the food would in all ordinary cases be more than sufficient to cover the deficiency of salts in the water. The statements, which are occasionally made, that the drinking of distilled water leads to toxic effects, are therefor entirely groundless: Distilled water is often drunk exclusively on ships, without any bad results.

3. **The Effects of Water Taken by Mouth.— Absorption.—** Water is rather slowly absorbed from the *stomach,* where it also delays the absorption of other substances. On the other hand, it is absorbed readily from the *intestine,* small and large; and in these it favors the absorption of dissolved substances.

The popular opinion that water can be absorbed from the *skin,* is not in accord with experimental evidence. The epidermis appears to be entirely impermeable to it. Bathing in cold water will contract the cutaneous vessels, and will in this way diminish the loss of water by perspiration; while hot water will increase the loss by favoring diaphoresis.

The **Excretion** of water occurs by the kidneys, lungs, skin, and intestine. The relative importance of these channels varies with conditions. If, for instance, the water is taken hot (so as to favor dilation of the cutaneous vessels), it will act as a *diaphoretic.* If the conditions are not favorable to diaphoresis, it will be excreted mainly by the kidneys. The **diuretic action** of pure water is quite prompt, strong, and certain — differing greatly from its weak effect on intravenous injection. (Probably because it is rendered isotonic in the course of its absorption, and before it reaches the kidneys.) The excretion of urine may exceed ten liters per day. The *urine* becomes very dilute, the constituents being diminished in percentage, but increased in absolute amount. The diuretic action of moderate quantities of water can be greatly enhanced by the addition of other diuretics, but if very large quantities of water are given, the addition of diuretics has no further effect.

Excessive quantities of water may also be excreted by the *intestine,* if the conditions are favorable, and may thus lead to diarrhea.

Digestion and Absorption of Food.— The drinking of moderate quantities of water favors these processes, increasing the secretion of hydrochloric acid, and hastening the passage of food through the pylorus. In health, however, very considerable variations of the water-income have but little effect on the utilization of food (Spiegler, 1901).

Metabolism.— The effects of water on the chemic processes in the body are important. The administration of large quantities of water cause a very considerable *temporary increase* in the urinary nitrogen, as much as 34% (Neumann, 1899). The excess is excreted mainly as urea; the uric acid being often unchanged. The excretion of the phosphates and sulphates is also increased. The removal of chlorids is so extensive, that their percentage in the urine soon falls to a very low figure.

The excessive excretion of metabolites is partly due, beyond doubt, to the "*flushing out*" of the tissues by the diuresis. But if this were the only cause, the continued excessive administration of water would soon exhaust the stored waste products, and their excretion would fall rather below the normal figure. Actual results show that this is not the case: The excretion remains permanently increased, although it does not remain at the original high figure (Edsall, 1900). There must therefore be an *increased production of these metabolites.* This conclusion is supported by the results on *animals,* although these are somewhat different from those obtained on man. Dogs in nitrogen equillibrium do not show any permanent changes in their nitrogen excretion when four times the normal quantity of water is administered, notwithstanding the increased diuresis. In starving dogs, however, it may be increased by 80%. The explanation of these discordant results is probably, that the removal of the water by diuresis keeps step with the absorption in the fed animals; so that it never comes to any considerable increase in the water content of the body, and the metabolism is therefore not increased.

It is a remarkable fact that the administration of very large quantities of water (to 10 L. per day), continued for several weeks, is apparently *without deleterious effect,* and does not even create salt hunger (Cushing and Clarke, Sollmann and Hofmann, 1905).

Therapeutic Uses of Water.— The *external use* of water rests mainly on the reflex effects of temperature, etc., and will be discussed in another place.

The *internal use* of large quantities of water is advisable in the treatment of certain dyspepsias. It is especially valuable, however, for its diaphoretic and diuretic effects. The special indications of diaphoresis and diuresis are discussed elsewhere (see index).

The *changes in metabolism* (the "alterative effect") is utilized in a variety of obscure conditions supposed to be connected with disturbance of these functions. Weak mineral waters act mainly in this manner. This action is employed particularly in *obesity,* but the results are uncertain.

It is difficult to say beforehand whether the breaking-down of proteid molecules will increase or diminish the body fat. If it is only partial, it may result in the formation of fat from the proteids; if carried further, it may lead to the destruction of fat as well.

Cushing (1905) has found the administration of very large quantities of cold water (four ounces every fifteen minutes whilst awake) of very marked benefit in *typhoid fever.* It serves to keep the mouth clean; it must have a distinct antipyretic effect; and it may aid by eliminating toxins and waste-products.

The use of water as a vehicle must be mentioned. It is very important that soluble substances be given in sufficiently dilute solutions, when it is desired to obtain their remote action to the exclusion of a local action.

4. The **withholding of water** affects the metabolism in much the same way as the administration of salts in hyperisotonic solution: The excretion of metabolites is at first lowered, by the lessened

diuresis; but as the destruction of proteids is at the same time increased, their excretion is also increased after a time. When water is again given, the stored metabolites are washed out, leading to a very greatly increased excretion (Landauer, 1895; Straub, 1899; Spiegler, 1901).

Aqua (U. S. P.).— Potable water in its purest obtainable state. The limits of impurities are laid down.

Aqua Destillata (U. S. P.).—*Distilled Water.*—The first tenth of the distillate is rejected, the next four-fifths being collected.

VI. EFFECTS OF SALTS.

The immediate effects of salts differ with the quantity and dilution, and especially with the channel by which they are introduced. They can be best studied on sodium chlorid which does not possess specific actions in any marked degree.

Intravenous or Subcutaneous Injections of Nearly Isotonic Solutions.— The general effects on the quantity of blood, on the lymph-flow, and on the urine have been discussed. The increased quantity of blood produces a very moderate rise of blood-pressure; and this, perhaps with some direct salt-action, results in an increased excitability of the respiratory, vagus, and vasomotor centers.[1] With *normal animals,* the rise of capillary pressure is large and persistent; whilst the rise of arterial pressure and the medullary stimulations pass off quickly, but without noticeable fatigue. In *animals whose blood-pressure is* low — particularly if this is due to hemorrahge,[2] saline infusions bring the pressure toward normal, and maintain it quite effectually (see Fig. 51). Excessive injections of saline solutions may cause death from *pulmonary edema,* or from overdistention of the heart. They may also produce glycosuria and rarely albuminuria.

These effects are produced by all salts whose ions are not specifically toxic, *e. g.,* by most sodium salts. To have any effect, these must be used in rather large amounts, *i. e.,* from 25 to 50 c. c. of the eighth-molecular solution per Kilo body weight. Solutions which contain *all* the salts of the serum in the proper proportions (*e. g.,* Locke's Fluid) are somewhat better than the normal (0.9%) sodium chlorid solution, but the latter suffices for all practical purposes. The *transfusion of serum or blood* has few advantages, and a number of dangers.

Hyperisotonic Solutions, by abstracting water from the tissues, produce a much more violent stimulation of the central nervous system, passing on to convulsions, but always followed by depression. The blood-pressure shows a progressive fall, with temporary rise during the spasms. The respiration is at first quickened, but becomes slow and shallow as the blood-pressure falls. The heart is quickened, feeble, and arythmic. In the later stages it may be slowed by stimulation of the vagus center. The temperature rises.

The diuretic effect and the local irritation are also much greater.

It is probable that some of the phenomena of *uremia* are due to a hyperisotonic condition of the blood, which may reach almost double the normal concentration, in this condition.

Hypoisotonic Solutions act very much like isotonic solutions, but are somewhat more injurious and may lake the blood.

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[1] Exercise 62.

[2] In dogs, a *loss of blood* of less than 2% of the body weight does not lower the blood-pressure for longer than ten minutes. 2% lowers it for an hour. The pulse rate is increased; this may be followed by a slight slowing. Larger doses produce the phenomena of asphyxia.

Therapeutic Uses of Saline Injections.— These are utilized mainly in two conditions: in shock and in toxemia (nephritis, eclampsia, infections, and ordinary poisons). Their use in the latter condition rests on the removal of the poison by the diuresis.[1] Saline injections are *contraindicated* when there is a tendency to pulmonary edema; they must also be used cautiously in anuria, and must not be persisted in if a moderate injection does not cause diuresis.

VII. SALTS TAKEN BY MOUTH.

Local Actions.— Salts in isotonic or hypoisotonic solutions have little local action; in substance or in hyperisotonic solutions they act as rather mild irritants, without destroying the tissues.

(a) An extensive stimulation of the **skin,** produced in this manner, and the reflexes which arise from it, explain the effects of sea and salt baths.

(b) They exert a similar stimulation upon the walls of the **alimentary canal.** This will be seen principally in the *stomach* before they suffer dilution. Their action here is a deep one, since they will stimulate all the cells with which they come into contact in the course of their absorption. Since they are quickly removed by further absorption, they do not cause any permanent change. In this way they differ from the majority of gastric irritants, which produce a superficial but persistent action. The stimulation by salts may, therefore, be continued for a considerable time, and is frequently very useful in the treatment of certain cases of "atonic" *dyspepsia.*

If salts are given in large amounts and concentrated form, the irritation may lead to a strong inflammation — to severe *gastro-enteritis,* which may be fatal in the case of some salts (see Potassium Nitrate).

(c) Action After Absorption.— The ingestion of salts, without sufficient water to render them isotonic, must tend to *increase the salt-concentration of the body.* This increase affects mainly the tissues, the molecular concentration of the blood remaining practically unaltered. This increased salt-concentration is counteracted by the stimulation of two mechanisms: a desire for water (*thirst*); and the elimination of highly *hypertonic urine.* If water is given freely, the salts are powerfully *diuretic.* This leads to an *increased excretion of metabolites,* partly by the flushing out of stored waste-products, but also by *direct stimulation of metabolism.* This *alterative action* is especially pronounced in the case of salts which are foreign to the body (potassium iodid), since they alter the composition of the cells more profoundly than an equivalent quantity of a normal salt. Potassium salts are therefor always preferred to those of sodium to secure an alterative effect.

3. **Therapeutic Uses.**— The effect upon the *metabolism* is uncertain in its outcome, as is the case with all alteratives. It may be useful especially in *obesity.*

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[1] The following mixture has been recommended as especially diuretic (S. A. Mathews, 1904): $NaCl$ 3.67; Na_2SO_4 10.1; Sod. Citr. 3.36; $CaCl_2$ 0.136; water ad 1000. 600 c. c. are injected intravenously in 2½ hours (at the rate of 3 c. c. per minute); the injection may be repeated daily.

The *diuretic* action is a very useful one. Its extent will be proportional to the amount of salt introduced. The latter is limited by the tendency to gastric irritation. The salt which has the least of this unpleasant side-action is potassium acetate.

The irritant action upon the *stomach* is useful in some cases of dyspepsia. Small doses are used for this purpose.

With larger doses a nauseant and *emetic* action appears, and may be useful.

If the salts themselves are readily absorbed, they will increase the *rapidity of absorption* from the intestinal canal. If they are not readily absorbed, they will act to some extent as *cathartics.*

Since the action of salts on blood causes the precipitation of globulins, they may be employed as *local hemostatics.* By the withdrawal of water they render the conditions unfavorable to the development of bacteria, and are, therefore, used as *preservatives for meat,* etc.

VIII. SALT HUNGER.

The maintenance of a certain salt-content is indispensable to the body, sodium chlorid being especially important. Animal food appears to contain a sufficiency of this salt; whilst a herbivorous and omnivorous diet is insufficient in this respect. Under ordinary conditions, the excretion of salt keeps perfectly parallel with the salt-income (Falk, 1848), so that a moderate excess of salt-income is practically without effect, except on the urine. A very limited salt-income (as by an exclusive milk diet) can also be borne for a considerable time, being met by a corresponding decrease of chlorid excretion, so that the percentage of the salt in the blood is scarcely altered, and no general symptoms whatever result.

If salt is withheld entirely (by starvation, or by giving food previously extracted with boiling water), the tissues and blood gradually lose chlorids (the urine continuing to eliminate traces until death). The free hydrochloric acid also disappears from the gastric juice. Very severe symptoms result. The animals emaciate rapidly, through anorexia and other interference with digestion and absorption. Great muscular weakness and tremors, with occasional convulsions, are very prominent. The mental faculties are dulled. The urine and breath contain acetone. Death occurs after a variable period (J. Forster, 1873). In man, an abstinence of nine days is serious, but not dangerous. The subject does not return to normal for a week or two after resuming the consumption of salt (E. Taylor, 1904).

The urinary chlorids are also diminished in fever. This is to be attributed in part to the limited salt-income of the usual fever diet; but the retention is much greater than in health, for unknown reasons (Garratt, 1904). The acute retention in pneumonia is due partly to the storage of salt in the effusion.

Sodii Chloridum (U. S. P., B. P.).—*Sodium Chlorid* (Common Salt). $NaCl$. Soluble in 2.8 parts water, almost insoluble in alcohol. A strong solution is used as emetic.

* *Urea.*—$CO(NH_2)_2$. Readily soluble in water and alcohol. White crystals. *Dose* (diuretic): 0.6 to 1.3 Gm. (10 to 20 grs.).

Glycerinum, Saccharum Lactis.—See Index.

(B) CATHARTIC SALTS.

1. MANNER OF ACTION.

A number of salts are not absorbed readily from the alimentary canal. These cannot produce the effects described above, unless they are injected into the circulation. When they are given by the mouth, their direct action is confined to the intestine: they produce *catharsis* with soft or fluid, painless stools. Through the catharsis they may produce, indirectly, a drying of the tissues and a slight increase of gaseous metabolism. The cathartic action is mainly the result of the retention of fluid in the intestine by the osmotic action of the unabsorbed salt, for this must retain sufficient fluid to preserve itself isotonic with the blood (Wallace and Cushny, 1898).[1] It is probable that this action is supported by a direct stimulant effect of the salt ions.

The fluidity of stools would in most cases be due to the non-absorption of fluid already present in the intestine. But should this be insufficient, fluid would also be drawn directly from the tissues. None of the cathartic salts are probably altogether unabsorbable; their absorption is favored and their cathartic action correspondingly lessened, if they remain for a long time in the alimentary canal. This is apt to occur if the tissues are very dry.

Recent investigations (J. B. MacCallum, 1903) have shown that most cathartic salts also increase peristalsis and the secretion of intestinal fluid very greatly when they are injected intravenously in isotonic solutions, or applied to the peritoneal surface of the intestine; more slowly if they are administered subcutaneously. The effects seem to be greater and more prompt than could be accounted for by the excretion of these salts into the intestine, so that it must be assumed that these ions produce a *direct irritation*. It is also suggestive that the same ions increase the irritability of most other tissues; and that their action on the intestine is abolished by calcium chlorid, which similarly inhibits their action on the other tissues.[2]

It would be useless to discuss the question whether the general salt action or the specific irritant action is the more important, since both tend to the same results. In the case of magnesium, where they act in an opposite sense, the osmotic action certainly predominates over the ion-action.

2. ABSORBABILITY OF IONS.

Any soluble substance must be conceived as capable of producing a salt catharsis in proportion as it is non-absorbable. But this may be modified or abolished by other factors.

Of non-absorbable ions, the ***heavy metals*** and ***alum*** produce a precipitation of proteids, and in this way an irritant or astringent effect. The earthy metals, Ca, Sr, Ba, are converted into insoluble carbonates. Oxalates and Fluorids are specifically toxic to protoplasm.

The *absorption of the more important Ions* is as follows: (a) Of the *Cathions* ammonium is the most readily absorbed; then come the other alkali metals. The earthy metals are not absorbable, but magnesium is practically the only non-absorbable kation which can be utilized as a cathartic.

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[1] Exercise 63.

[2] Exercise 46V.

(*b*) Of the *Anions,* the chlorids, bromids, iodids, and acetates are rapidly absorbed. The sulphates, phosphates, tartrates, citrates, lactates, and malates are comparatively non-absorbable, and therefore possess cathartic properties.

(*c*) Of *non-dissociable compounds,* which are soluble and non-absorbable, mention may be made of certain sugars, especially mannite; as also gums and pectins.[1]

Why certain ions should be capable of absorption, others not, cannot be satisfactorily explained. Although recent investigations have shown some striking analogies between the absorption of ions by the intestine and by muscle, and the solubility of their soaps and calcium salts, it is not yet clear whether this is a mere coincidence or has a deeper meaning.

3. THERAPEUTIC USES.

The general indications for cathartics will be discussed in Chapter XXX, E.

The cathartic salts differ from vegetable and metallic cathartics in causing much less local irritation. They are therefore especially useful in general inflammatory conditions, such as fevers. They do, however, produce some irritation, and if the alimentary canal itself is the seat of inflammation, this must be reduced to a minimum. This may be done by giving them in dilute solution — such as they exist in the natural aperient mineral waters — Hunyadi or Carlsbad, etc.

They also exert an irritant action on the *stomach*, if they remain in it for a considerable time. For this reason they should be avoided with bedridden patients, for with these the passage of food from the stomach to the intestine is a rather slow one. Some exercise is always useful after taking salts, and this is one of the reasons why patients receive benefits from salt-cures in watering-places which they fail to secure at home.

Because of this slight irritation, they are preferred for the removal of liquid from the body. The addition of a small amount of a vegetable cathartic — rhubarb or senna —

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[1] The latter have such a large molecular weight that they cannot exert any great salt action, but produce catharsis mainly mechanically by their own bulk. They form the *laxative principle of many fruits;* other fruits contain mannite or non-absorbable acid salts, tartrates, or malates.

seems very useful. The "black draft" or compound infusion of senna, is a very good preparation.

Just as all other cathartics, they are of use in *intestinal putrefaction,* by removing the putrefying mass.

The *choice between the salt cathartics* is very largely determined by their *taste.* The sodium sulphate has, perhaps, the most disagreeable taste; the magnesium sulphate somewhat less so. Sodium phosphate is perhaps the least disagreeable. MgO and $MgCO_3$ act as alkalies as well as cathartics.

We may now take up these salts somewhat more in detail.

4. SODIUM SULPHATE.

This is the most typical of these cathartic salts, being but very little absorbed, and almost free from ion action. It has no action on metabolism. On account of its very bitter taste, it is not much used, except in veterinary practice, but it forms an important ingredient of many mineral waters, *e. g.,* Carlsbad.

The kidneys are even more permeable to sodium sulphate than to NaCl, so that its intravenous injection produces a copious diuresis. The secretion of gastric juice is not increased.

The *stimulant action* of hypodermic or intravenous injections of sodium sulphate appear to surpass those of sodium chlorid, especially in phenol poisoning.[1] An isotonic solution (2% of the dried or 4% of the crystalline salt) is used in quantities of 500 to 1,000 c. c.

5. SODIUM PHOSPHATE.

The phosphates also exhibit merely a local cathartic salt action. The presence of phosphorus in nerve tissue suggested the use of phosphates and phosphoric acid as nerve stimulants. There seems to be no scientific foundation for this. The phosphoric acid of the urine comes almost entirely from the phosphorus of the nucleins of the cells, not from food, and it is doubtful whether the small amount of phosphates absorbed is ever utilized.

When injected subcutaneously, they are rapidly excreted by the intestine and kidneys. The feces contain phosphates even in starvation. Milk contains a large proportion of phosphates, and it is possible that the administration of these salts might be useful in lactation, but this has not been demonstrated. The administration of phosphates has no effect on nitrogen metabolism. Intravenously, the phosphates stimulate the vagus endings similarly to thyroiodin, and they have been claimed to be of benefit in the same conditions.

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[1] Exercise 59.

6. MAGNESIUM SALTS.

Magnesium salts are converted into the acid carbonate in the small intestine, according to the formula:

$$MgSO_4 + Na_2CO_3 + H_2O + CO_2 = Mg(HCO_3)_2 + Na_2SO_4.$$

In so far, it is quite immaterial what particular salt be given. The hydrate, carbonate, chlorid, or sulphate are all converted into this carbonate. However, in the case of the sulphate, the sodium sulphate which is formed is, of course, also cathartic, so that the effect is doubly large. The hydrate and carbonate, on the other hand, possess also the action of alkalies.

When taken by the mouth, magnesium is never absorbed in sufficient amount to have any ion action. Injected intravenously, it produces much the same effects as potassium: paralysis of the heart and the central nervous system.

These are sometimes seen in animals when the solution contained in the manometer inadvertently enters the circulation. They are usually not very lasting, since the excretion is quite rapid.

Magnesium Anesthesia.— Meltzer and Auer (1905) have found that a general anesthesia, with abolition of reflexes, may be produced by the subcutaneous injection of magnesium salts (1.5 Gm. of crystalline magnesium sulphate per Kg. of body weight, used as 25% solution). The injection causes but little pain, since the magnesium is also a local anesthetic. The anesthesia is complete in half an hour or an hour, and lasts about two hours. The blood pressure is but little lowered; there is some diuresis, but no diarrhea. The recovery is perfect. Somewhat larger doses are fatal, paralyzing the respiration before the heart. The effective dose approaches the fatal so closely that this method is not available for man. Meltzer has, however, used the *intraspinal method* (1 c.c. of 25%) successfully in several cases, and also in traumatic tetanus. This produces sensory and motor paralysis of the legs and pelvic region, occurring in 3 to 4 hours, and lasting 8 to 14 hours. There is also retention of urine for one or two days.

7. FERRO- AND FERRI-CYANIDS.

These belong to the typical non-absorbable salts, and are entirely free from cyanid action. They are not, however, employed as cathartics, since the HCN could conceivably be liberated from them by acids. They have, indeed, been very little studied.

Ferrocyanids form insoluble precipitates with most metals (Cu, Ni, Fe, Co, Zn) and with Strychnin, and have been suggested as chemic antidotes to these poisons.

MATERIA MEDICA OF CATHARTIC SALTS.

The *dose* of these, unless specially noted, is 4 to 30 Gm. (1 to 8 drachms) (teaspoonful to 2 tablespoonfuls) taken before breakfast in a tumbler of cold water. Doses of 0.5 to 1 Gm. (7½ to 15 grs.) are mildly laxative. They are practically *insoluble in alcohol.*

Crude Salts.

	One part of salt is soluble in water.
Magnesii Carbonas (U. S. P.).— $(MgCO_3)_4.Mg(OH)_2 + 5H_2O$ ... (3 Gm. = 45 grs., U. S.P.)	Pract. insol.
Magnesii Carbonas Levis and *Magnesii Carbonas Ponderosus* (B. P.)...	" "
Magnesii Oxidum (U. S. P.) [*Magnesia Levis,* B. P.].—*Light Magnesia* ... MgO. *Dose:* 2 Gm. = 30 grs., U. S. P.	" "
Magnesii Oxidum Ponderosum (U. S. P.) [*Magnesia Ponderosa,* B. P.].—*Heavy Magnesia* ... MgO. *Dose:* 2 Gm. = 30 grs., U. S. P.	" "
Magnesii Sulphas (U. S. P., B. P.).—*Epsom Salt.*— $MgSO_4 + 7H_2O$ ...	0.85
Potassii Bitartras (U. S. P.) [*Potassii Tartras Acidus,* B.P.].—*Cream of Tartar.* $KHC_4H_4O_6$... *Dose* as diuretic: 2 Gm. = 30 grs., U. S. P.	200.
Potassii et Sodii Tartras (U. S. P.) [*Soda Tartrata,* B. P.].—*Rochelle Salt.*— $KNaC_4H_4O_6 + 4H_2O$ ...	1.2
Potassii Sulphas (U. S. P.).— K_2SO_4. *Dose:* 2 Gm. = 30 grs., U. S. P...	9.
Sodii Phosphas (U. S. P., B. P.).— $Na_2HPO_4 + 12H_2O$. *Dose:* 2 Gm. = 30 grs., U. S. P...	5.5
Sodii Phosphas Exsiccatess (U. S. P.).— Na_2HPO_4. *Dose:* 1 Gm. = 15 grs., U. S. P...	
Sodii Pyrophosphas (U. S. P.).— $Na_4P_2O_7 + 10H_2O$. *Dose:* 2 Gm. = 30 grs., U. S. P...	11.5
Sodii Sulphas (U. S. P., B. P.).—*Glauber's Salt.*— $Na_2SO_4 + 10H_2O$ ...	2.8

Saccharum Lactis (U. S. P., B. P.).—*Milk Sugar.*— Prepared by evaporating and crystallizing the whey of cow's milk. $C_{12}H_{22}O_{11} + H_2O$. Hard white crystalline masses or powder. Sol. in 4.79 water, insol. in alcohol. 9 to 15 Gm. (2 to 4ʒ), in warm milk an hour before breakfast, causes a soft stool. Smaller doses (pure or as milk) are efficient for diuresis. Milk Sugar is also used to facilitate the comminution of powders, on account of its hardness. It is further employed as sweetening agent, especially for powders; and in infant foods.

The *Citrates* are considered in Chapter XXV (see Index).

Effervescing Salts.

Pulvis Effervescens Compositus (U. S. P.) [*Pulvis Sodæ Tartratæ Effervescens,* B. P.].—*Seidlitz Powder.*—The blue paper contains Rochelle Salts (7.5 Gm.) and Sod. Bicarb.; the white, tartaric acid. Each is to be dissolved separately in a little water, the solution mixed in a large tumbler, and drunk whilst effervescing.

The dose of the other effervescent salts is one to two teaspoonfuls, dissolved in cold water when needed, and drunk immediately. All the above salts are prepared in effervescent form by manufacturers. The following are official in the respective Pharmacopœias:

U. S. P.

Magnesii Sulphas Effervescens — 50%.
Sodii Phosphas Effervescens — 20% of exsiccated.
Lithii Citras Effervescens — 5%.

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B. P.

Lithii Citras Effervescens.
Magnesii Sulphas Effervescens.
Sodii Citro-tartras Effervescens.
Sodii Phosphas Effervescens.
Sodii Sulphas Effervescens.

Liquid Preparations.

Liquor Magnesii Citratis (U. S. P.).— An effervescing solution, put up in bottles of 360 c.c. (12℥), containing 15. Gm. (½℥) of Magnesium Carbonate, dissolved by Citric Acid. *Dose:* one bottle, in divided doses.

Liquor Magnesii Carbonatis (B. P.).— A 2% carbonated solution. *Dose:* 30 to 60 c.c. (1 to 2 ozs.).

Liquor Sodii Phosphatis Compositus (U. S. P.).— 100 c.c. of the solution contains 100 Gm. of sodium phosphate, 4 Gm. of sodium nitrate, and 13 Gm. of citric acid. *Dose:* 8 c.c.=2ʒ (U. S. P.).

C. DIURETICS.[1]

Diuresis (increase of the quantity of urine) is produced by many substances acting by various mechanisms, and belonging to different groups. The whole subject may, however, be summarized in this place as a considerable proportion of the diuretics act, at least in part, by salt action.

The details of the actions of diuretics will not be discussed in this summary. They may be found by referring to the individual drugs.

Diuretics may be divided into the following classes:

1. Acting through changes in the general circulation.
2. Acting purely by local, irritant stimulation of the kidney-cells.
3. Acting by non-irritant stimulation of the kidney-cells.
4. Acting mainly by salt action.

1. Diuretics Which Act by Influencing the General Circulation.— The secretion of urine is roughly proportional to the glomerular blood-pressure. This may be raised by increasing the work of the heart, as by *Digitalis* (which acts also by increasing the pulse-wave, lessening venous congestion, and rendering the blood hydremic). Vasoconstrictors generally act very powerfully on the renal arterioles, so that they tend to lower the glomerular pressure, notwithstanding the rise of general blood-pressure. Vasodilators also tend to lower the glomerular pressure. They are useful, however, when a vasoconstriction is to be counteracted, as with Digitalis or Caffein.

2. Irritant Diuretics.— *Moderate irritation* raises the glomerular pressure by dilating the renal arterioles. It is conceivable that it also stimulates the vital secretory activity of the cell. *Excessive irritation,* on the other hand, produces venous congestion, which hinders the filtration of urine by compressing the tubules. The cells are also injured, as shown by the appearance of albuminuria; and their permeability is thereby lessened.

Irritant diuretics are very numerous and only a few of the more important can be mentioned:

(*a*) *Essential Oils.*— Especially turpentine, juniper, cubeba, etc.

(*b*) *Hydrocarbons.*— Alcohol, urethane, urotropin, etc. These produce only a mild irritation.

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[1] Exercises 64, 65, 69 to 72.

(The diuretic action of beer is due mainly to the rapid ingestion of its water; at least, Rapael (1894) failed to discover any difference in the daily excretion, whether a liter of water or of beer was taken.)

(*c*) *Absorbable Metals.*— Especially Calomel.

(*d*) *Aromatic Series.*— All the members of the series are diuretic, and this is commonly encountered as a side-action; it can be used practically only in a few instances, as with Uva Ursi and Piperazin.

(*e*) *Glucosids.*— These are closely related to the aromatic series. Here belong:

Broom Tops (Scoparius). These owe their diuretic action to Scoparin. The alkaloid Spartein (see Index) does not contribute to it. *Dose* of Scoparius (Extractum Scoparii Fluidum): 1.0 to 4.0 c.c.

Asparagus tops seem to act similarly. They are given in 4 c.c. doses of the fluidextract.

Corn Silk, Triticum, Guaiac, etc., may be counted in this group.

Cantharidin, Aloin, etc., are too powerful for therapeutic use.

(*f*) *Acids, Alkalies, and Some Salts* (*notably Nitrates*) are also mildly irritant.

3. **Stimulant Diuretics.**— This is the place generally assigned to caffein and theobromin; part of their effect, however, is due to peripheral dilation of the renal arterioles. No irritant action has been described for caffein and theobromin even for large doses; but it has been noted with theocin. However, large doses of caffein interfere with diuresis by central vasoconstriction. This is to be counteracted by chloral or nitroglycerin.

4. **Saline Diuretics.**— Water, salts, sugars, urea, etc., act by lessening the viscidity of the blood, thereby increasing its filtrability and raising the glomerular pressure; by shrinking the renal cells; and by preventing the reabsorption of water from the tubules. In addition, it is rather probable that they cause the stimulation of the vital activity of the kidney-cells. This is most pronounced in the case of milk-sugar; urea; iodids; nitrates; alkalies; and acids.

Water may be rendered more palatable by carbonic acid, or by giving it as lemonade, or as teas. These additions enhance its diuretic effect.

Normal Saline solution may be injected hypodermically or by rectum. The following mixture has been found to produce an especially large diuresis, and has been recommended for the removal of toxins, etc. (S. A. Mathews, 1904): $NaCl$, 3.67; Na_2SO_4, 10.1; $CaCl_2$, 0.136; Sod. Citrate, 3.36; Water, 1,000. 600 c.c. per day of this are injected very slowly into a vein (3 c.c. per minute).

Milk is a very efficient diuretic, acting partly by its water, partly by its sugar. Milk-sugar and Urea are given in doses of 10 to 30 Gm.

Diluted Inorganic Acids (in the form of lemonade) are rather too irritant to the stomach and kidneys, and are to be used only if an acid action is distinctly indicated.

Alkalies are very effective; they also render the urine alkaline. Free alkalies and carbonates are not used, since they interfere with digestion. The effect is obtained from *organic acids and their salts* (especially the acetate or citrate of potassium), which are oxidized to carbonates in the body.

Iodids and Nitrates are given as the potassium salts. The iodid acts too powerfully on other functions to be used as a pure diuretic. The reputation of lithium is unmerited.

The **comparative diuretic effect** of these drugs on normal man was investigated by Raphael (1894), who placed himself on a uniform diet for prolonged periods. He consumed daily 1,180 c.c. of fluid;

the quantity of urine on this diet amounted to 750—960 c.c. Under the influence of drugs, it was increased by the following percentage:

1,000 c.c. water — 100%.
1,000 c.c. carbonated water — 73%.
1,000 c.c. beer — 100%.
1,000 c.c. claret — 80%.
1,000 c.c. milk — 153%.
30 Gm. milk-sugar — 34%.
0.4 Gm. turpentine — 11%.
0.2 Gm. Ol. Junip. + 1,000 c.c. water — 111%.
0.5 Gm. Caffein-Sod.-Salicyl. — 42%.
0.5 Gm. Diuretin — 2%.
1.5 " " 14%.
3. " " 53%.

In *disease,* the results would probably not be quite the same. The choice of the diuretic must be determined by the condition of the kidneys, and by the object to be accomplished. A combination of several diuretics is often most effective; they are generally administered with plenty of water.

The **indications for diuretics** are as follows:

1. The *removal of liquid* from the body, in the various forms of dropsy. In this case it is well to employ them with as little fluid as possible.

If the dropsy is of *cardiac origin* drugs of the digitalis series, combined if necessary with nitroglycerin, are the most efficient diuretics, and salts may also be added. If it is of *metabolic origin,* benefits may follow salts or arsenic. If, however, it is of *renal origin,* diuretics should be avoided altogether, and recourse should be had to diaphoresis.

2. *To remove toxic substances from the organism,* whether these have been introduced from without or formed within the body, a free supply of water, in the form of infusions, supported by the irritants, salts, or theobromin, fulfils the indication. The hypodermic injection of large amounts of normal salt solution is a most effective method. Irritants must be avoided if the kidneys are inflamed, or if the poison is itself irritant.

3. *To dilute the urine:* This may be useful (*a*) to render it less irritant to the urinary passages in nephritis or inflammation of the bladder or urethra; it also serves a useful purpose in frequently washing out the pus and bacteria.

(*b*) To prevent the formation of calculi, or to remove concretions formed in the urinary tubules (as in oxalate-poisoning).

(*c*) To dilute irritant poisons, whose action on the kidneys is proportional to their concentration.

For the dilution of the urine, water supported by theobromin is of the greatest service.

Nephritis **contraindicates** irritant diuretics, and such as will become poisonous if they are not excreted (potassium, digitalis, mercury).

CHAPTER XXV.

ION ACTION OF SOLUBLE SALTS.

In addition to the osmotic actions which have just been described, electrolytes show effects which are due to their constituent ions. These actions are generally proportional to the degree of ionization: The comparatively firm mercuric albuminate is much less active than the ionized mercuric chlorid; ferrocyanids, in which the iron does not exist as an ion, acts quite differently from ferrous salts, and these again differ from ferric salts. Gaseous chlorine does not behave at all like the chlorine ion of NaCl; etc. The chemic behavior varies in the same way with the degree and state of ionization. The ions may act by entering into chemic combinations with the protoplasm, producing various compounds, syntheses, and decompositions, and thereby lead to functional changes. They may also alter the permeability of the cell-wall. Besides these chemic actions, it appears more than probable that the electric charges carried by the ions exert actions which are independent of the chemic nature of the ions. These latter actions may well be termed "*electron-actions*,"[1] whilst the sum of the chemic and electric actions produced by the ions may be grouped together as "*specific ion actions*." It is quite conceivable that the chemic actions are also in the last instance resolvable into electric manifestations. But since the proof for this has not yet been furnished, and since the two classes of actions exhibit striking differences, it is well to keep them apart, in so far as this is practicable.

A. ELECTRON ACTIONS.[2]

By this term we understand those actions which are produced by the electric charges carried by ions. These modify the electric condition of the protoplasmic colloids, and hence their viscidity. This leads to important modifications of functions.

The existence of these actions is shown by the fact that all electrolytes produce certain effects in common, which are not produced by non-electrolytes. For instance, an egg-albumin solution cannot be coagulated by heating when the electrolytes have been removed by dialysis. The coagulability is restored by the addition of electrolytes, but not by non-electrolytes (sugar, etc.). These effects are largely independent of the chemic properties of the ions, but vary with their electric properties, such as the sign of their electric charge and the ease with which they part with this. The effects agree with those of positive and negative electric stimulation; anions and cathions tend to produce opposite effects, the action of an electrolyte being determined by the predominating ion; analogous phenomena are exhibited when electrolytes are added to solutions of colloids.

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[1] Many authors use the term "ion actions" to designate what is here called electron-actions.

[2] Consult Exercises 46 and 70. Consult pages 520 and 528.

A solution containing a single electrolyte, no matter what the chemic nature of the latter, is fatal to all forms of life. This toxicity can be greatly lessened by the addition of a second salt; for perfect functionation, several salts are necessary, in a definite "balanced" ratio; departures from this ratio modify the functions of the cell, and larger changes are fatal. The mineral constituents of cells are therefor indispensable to life.

Proofs of the Existence of Electron Action.—J. Loeb (1902), to whom we are mainly indebted for the physiologic conception of the electron actions, reasoned from the well-known stimulant effects of galvanic electricity, that the electric charges of ions should also have corresponding effects. This presumption has been well supported by the experimental results on living organisms, and is explained by the physical researches on colloids, as has been indicated in the preceding chapter.

To demonstrate the electron action, it was necessary, first of all, to eliminate osmosis. This may be done by employing isotonic solutions, or by experimenting on animals which are not affected by osmosis. For instance, a small fish, Fundulus, and its ova, have a most remarkable resistance to osmotic changes, living quite well in distilled water, and in sea water the molecular concentration of which has been more than doubled. It will die, however, if it is placed in a solution of any single salt; but not in solutions of non-electrolytes.

It was much more difficult to exclude ordinary chemical changes as the cause of the phenomena which might be attributed to electron action. Even now, a complete separation of the two is not possible; but the connection between the electric properties of the ion and its physiologic action, suffices to establish the existence of electron actions.

The effect of electrolytes on colloidal solutions is one of the most convincing proofs of electron action. These phenomena were investigated by Hardy (1899 and 1900). It was stated on page 521 that the colloid aggregates are kept in solution by their electric charges. These are not at all influenced by the addition of non-electrolytes, such as sugar or urea. But they are increased or diminished by electrolytes. Colloids with negative charges are precipitated by cathions and rendered more fluid by anions, and vice versa. The action of different ions of the same sign differ quantitatively. This can be studied by comparing the effects of different anions combined with the same cathion, in equimolecular solutions, and vice versa. It *increases generally with the valency. H and OH* are also very strong ions, so that acids act as cathions, alkalies as anions. *The action of* *an electrolyte equals the algebraic sum of the action of its ions.* For instance, if the strength of a cathion "A" is expressed as +2, of an anion "B" as —1, and of anion "C" as —4; then a salt "AB" would have an action of +1; "AC" of —2. By the use of this method, Pauli (1903) has found that for egg albumin the cathions Mg, NH_4, K, Na, and Li precipitate in this order (Li most); whilst the anions prevent the precipitation in the order: $C_2H_3O_2$, Cl, NO_3, I, SCN (the last having the greatest solvent action). The effect would be the reverse if a positively charged colloid were employed in place of the negative albumen. A. P. Mathews (1905) has found that the precipitative power is in close agreement with his theory of solution-tension (see below).

The reaction of motor-nerves to electrolytes has also been shown to be an additive function of the two ions: the anions (alkalies or increase of valency) stimulating the sciatic nerve of the frog, whilst cathions (acids) lower its irritability (A. P. Mathews, 1902). This agrees with the old observation of Galvani (confirmed by Grandis, 1902), that the nerve is stimulated when it is charged by induction with negative electricity, and depressed by a positive charge. Mathews assumes that the stimulation is caused by the precipitation of the (positive) colloids of the nerve by the anions, and vice versa. This demands further proof, especially before it is extended to other forms of protoplasm.

The Relation of the Toxicity of Ions to Their Electric Properties.— The quantitative effects of ions on protoplasm can be estimated most exactly and most conveniently by observing the molecular concentration in which the solution will just cause death. This has been studied by a number of investigators. It was noticed that the *toxicity increases generally with the atomic weight* of the ion — Hg, for instance, being much more toxic than Na; but, on the other hand, H was found more toxic than the heavier Na. The *toxicity also increases generally with the valency;* but here also there are very striking exceptions, the monovalent Ag being more toxic than the trivalent Al. The general rule is so striking, both as to the atomic weight and valency, that some connection could not be doubted; but it is evidently not a simple one. The subject has been very greatly elucidated by the extensive experiments of A. P. Mathews (1904) on fundulus eggs, which are peculiarly adapted to these investigations. These showed a remarkable agreement between the toxicity and the solution-tension of ions.

The **solution-tension** signifies the tendency of a metal to go into solution, and thus to acquire an electric charge. This may be estimated by physical methods. The greater the solution-tension, the greater is the affinity of the ion for its charge; the less apt will this ion be to part with its charge, and therefor, the less its effect on colloids. This is precisely what Mathews found: *the toxicity of an ion varies inversely as its solution-tension;* the toxicity of a salt varies inversely as its *"decomposition-tension," i. e.,* as the sum of the solution-tension of both its ions. (For instance, if the solution-tension of the anion is 1 and of the cathion 2, the decomposition-tension of the salt is 3.) The same law applies to the inhibitory action of electrolytes on ferments. Mathews also found that the toxicity increases with the quotient: equivalent weight divided by *atomic volume.* When we understand the electric condition of ions and colloids better, we shall probably find that there is a common basis to these connected phenomena; and some apparent exceptions, which still exist, will probably be explained.

Other forms of life do not show precisely the same correspondence *as does the fundulus egg.* The disagreement can be seen from the following figures:

THE TOXICITY OF:	FUNDULUS EGG (Mathews).	LUPINE ROOTS (R. H. True).
Ca : Na or K,	As 1 : 1	As 1 : 5
Ca : Mg,	“ 1 : ½	“ 1 : 200
H : Fe or Co,	“ 1 : 4	“ 1 : $^1/_{250}$
Ni : Cu,	“ 1 : 700	“ 1 : 1
Fe : Hg,	“ 1 : 20,000	“ 1 : 1

This disagreement could be expected from the *complicated conditions* which prevail in most cells, and does not at all speak against Mathews' law. The latter deals only with the affinity of the ion for its charge; but the colloid is also an active factor in the reaction, some *protoplasm* showing a greater affinity for positive charges, and others for negative charges. The factor of *penetration* introduces important complications. Electron actions must occur even when the ions do not penetrate into the cell, the charges being transferred through the intermediation of the colloidal cell-wall. This is indeed the most favorable condition for the study of electron-actions, since it excludes the possibility of chemic changes. It probably explains the comparatively simple results obtained with fundulus ova, for the experiments of O. H. Brown (1905) have demonstrated their comparatively great impermeability to salts and water. With most cells, however, the possibility of strictly *chemic modifications* of the protoplasm by the ions is more or less important. Finally, the action of the added ions will be greatly *modified by the ions which are already present* in the tissues, as will be seen in the next paragraph.

Antitoxic Action of Ions.— As far as known, no cell can remain alive unless it contains some electrolytes.[1] If these are reduced below a certain minimum, the cell dies rapidly. But in many cases it dies even more promptly if it is placed in a solution containing but a single electrolyte. This is the toxicity which was described in the preceding paragraph. It would seem therefor that *several electrolytes, in a certain ratio, are required in order that the cell may perform its functions.* This was confirmed by J. Loeb (1901), who showed that the toxicity of an electrolyte can be very greatly lessened by the addition of another electrolyte, sometimes in very small proportion. (For instance, the addition of $\frac{1}{4000}$m $CaCl_2$ neutralizes the toxic action of $\frac{5}{8}$m. NaCl on Fundulus ova.) The antagonism is mutual, at least to some extent.

From his observations, Loeb concluded that the cathions were responsible both for the toxic and antitoxic actions;[2] and that cathions of different valency neutralized each other. The extensive experiments of A. P. Mathews (1905) modify these theories: It would appear that cathions and anions are both concerned in the toxic and antitoxic actions (although the cathions are probably the more important); and that the valency has no direct connection with either the toxic or antitoxic action. The decomposition-tension seems to be of subsidiary importance in the antitoxic action, and it appears to be necessary to invoke several mechanisms, especially chemic, for its explanation. The antagonism is evidently a complex phenomena, involving also the **specific ion actions.** It may be noticed, for instance, that certain ions (NH_4 and Li) are particularly difficult to neutralize; Ca is especially antitoxic, Mg much less so; Ni scarcely at all. The optimum ratio and the degree of antagonism vary for different classes of cells. Even when the antagonism of two salts is at its best, it is never perfect; it requires the addition of one or more further salts to enable the cell to perform its functions properly. Indeed, *a strictly normal condition is not reached until the cell is placed in a solution, the cathions of which are within narrow limits the same qualitatively and quantitatively as those of its normal surroundings.*[1] Instances will be given in the succeeding paragraphs, that closely related ions sometimes have very different effects, and cannot replace each other. All these phenomena can be explained on the pure electron-theory only by making far-reaching assumptions, which are not yet justified. Neither can it be denied, however, that the electric charges may play an important part by modifying the viscidity, either directly, or through the occurrence of chemic changes which modify the electric condition of the colloid (Pauli, 1903, has observed, for instance, that the addition of calcium reverses the effect of anions on the precipitation of albumen). The addition of a second salt may also alter the ionic condition of the first, the calcium and citrate ions being mutually antagonistic in this manner (Sabbatani, 1901). G. N. Stewart (1903) suggests that the antagonism may be explained in some cases by alteration of the permeability of the cell-wall, preventing osmosis or the penetration of harmful ions. This is supported by some of Mathews' observations. Finally, the antagonism may be functional, for it has been noticed that calcium also antagonizes some poisons which are not electrolytes (veratrin, Ringer, 1884; physostigmin, S. A. Mathews and O. H. Brown, 1904; cascara, MacCallum, 1904), and to which it is opposed in its functional effects.

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[1] The microchemic investigations of A. B. Macallum (1905) indicate that the electrolytes are localized in certain portions of the cell.

[2] The term "antitoxic action," applied to ions, means something very different from the same term when it is used in connection with bacterial poisons.

Ion Effects on Muscular Tissues.—The irritability of muscle is closely connected with its ions, and any change in the latter influences the muscular functions. For instance, if a *skeletal muscle* is placed in an isotonic solution of an electrolyte with monovalent cathion, it exhibits *ryhthmic contractions* (Loeb, 1899); if a certain proportion of a calcium salt is added, the ryhthmic property disappears again. The ryhthmic contraction of the *cardiac muscle* or of medusæ also disappears when calcium is added. Rhythmic contractibility is not therefor a property characteristic of cardiac muscle, but is inherent in all muscular tissues. The reason why the contraction of the heart is ordinarily rhythmic, and that of skeletal muscle not, lies in the fact that the ions in the heart are balanced so as to favor rhythmic contractions, and in the skeletal muscle they are not so balanced. It had long been recognized empirically that the heart will only continue to beat in solutions which contain a number of electrolytes in a pretty definite ratio; a deficiency or an excess of any of these ions being equally fatal.[2]

Other functions of the muscle are also modified. Certain modifications of the ions lead to total *abolition of irritability.* Other modifications increase or lower the *tone* of muscle; or they may develop "*contact-irritability*," so that a muscle will react to stimuli which are ordinarily ineffective. The latter action may be concerned in the specific action of cathartic salts.

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[1] The following salt ions are absolutely necessary to plants: K, Mg, PO_4, CO_3 (Na and Cl are not necessary); Ca to all but the lower fungi and algæ. Mn forms an essential constituent of vegetable oxidizing enzymes. $NO_3$and SO_4 act as nutrients.

Animals require Na, Cl, CO_3, Ca, K, Mg, I, Fe, PO_4, SO_4. It is very doubtful whether other elements existing only in traces (such as Fl) are necessary, or merely accidental.

[2] *Ringer's fluid* (1884) was devised for the *frog's heart.* It is made by adding 1 c. c. of a *2%* KCl solution to 100 c. c. of 0.75% Nace solution which has been saturated with calcium phosphate. The *mammalian* heart requires a somewhat different ratio and a higher molecular concentration. It also demands the addition of nutritive material, and of oxygen. These conditions are fulfilled in Locke's Fluid (see Index).

R. S. Lillie (1902) has studied the effects of ions on the larvæ of a sea-worm (Arenicola), which executes both ciliary and muscular movements. He found that the presence of magnesium in the mixture favors the contraction of the cilia, calcium of the muscles; potassium hinders both. Parker (1905) has found that potassium reverses the stroke of certain cilia.

Ion Effects on the Kidneys.—The polyuria and glycosuria which follow the intravenous injection of large quantities of most sodium salts (especially in slightly hyperisotonic solutions) perhaps also involve ion action; at least (W. H. Fischer and O. H. Brown, 1903) the addition of a small proportion of $CaCl_2$ stops the *diuresis,* which may then be started again by injecting sodium acetate. Sr or Ba salts prevent the *glycosuria* without affecting the polyuria.

Sollmann (1905) has found that calcium also hinders the filtration of urine and impedes the circulation in excised kidneys, whilst magnesium favors them. These effects may be referred to ion actions on the renal protoplasm. The effects of most other ions which were investigated in this manner are referable to osmotic changes, due to differences of penetrability.

Importance and Limitations of the Electron Theory.—The theory of electron actions has furnished us with new and fruitful conceptions, with a deeper insight into the reactions of protoplasm, and with new indications of research. It should be remembered, however, that it does not as yet attempt to explain the actions of non-electrolytes; and that it cannot be said to explain fully all the actions of electrolytes. It does not, for instance, explain the qualitative differences in the action of the iodids, bromids, and chlorids; of calcium, magnesium, or barium; the specific toxicity of potassium for muscle and nerve; nor the need for the presence of several ions. We must not forget that protoplasm has chemical, as well as physical, properties; and that many, if not all, ions are capable of entering into ordinary chemical reaction with the protoplasm. The specific ion actions, as we can observe them, are therefor the result of a coöperation of physical and chemical changes. In the present state of knowledge, it would be unremunerative to attempt to distinguish between these. A more practical conception of the action of the individual ions can still be obtained by describing the phenomena as they are observed, without trying, as a rule, to penetrate into their meaning.

Only some of the ions will be discussed in this place; the acids, bases, metals, the cyanids, nitrites, the cathartic salts, etc., deserve special chapters.

B. SPECIAL ION ACTIONS.

Summary of Effects.—From the therapeutic standpoint the anions are the more important ions, the cathions being used mainly to modify the effects of the anions.

Amongst the **anions,** Cl is indifferent under the conditions of the body. Br causes a depression of the central nervous system. I and SCN produce changes in metabolism; fluorid oxalates, and to a less extent citrates and tartrates, are toxic by immobilizing calcium; organic anions, carbonates and bicarbonates act as alkalies; NO_3, ClO_3 and MnO_4 are oxidizing, irritant, and alter the blood; borates kill bacteria; NO_2 causes vasodilation and methemoglobin formation; CN hinders ferment-action. The other anions are for the most part non-absorbable.

The modifications introduced by the **Cathions**[1] are as follows: Na is indifferent. Mn, K, Rb or Cs depresses the heart and central nervous system. Li forms soluble urates and produces gastroenteritis. NH_4 hastens the penetration of the anion, and has itself a stimulant action on the central nervous system. The earthy metals delay the liberation and absorption of the anion. Ca depresses; Ba causes stimulation of muscle; Mg has a cathartic action. Metals exert a local chemic action; many (as Hg) have a specific toxicity.

The effects of the ions differ very greatly, quantitatively, according to the channel by which they are introduced; indeed, many ions are excreted more readily than they are absorbed, so that they are quite inactive when given by mouth, whilst they may produce violent effects when injected into the circulation.[2]

Modification of the Dose of Salts According to the Cathion.—On account of the differences in absorption and by their specific actions, the cathions influence the doses of salts, generally as follows: Taking the dose of the sodium salts as 1, that of the NH_4 salt is ½; K, Rb or Li=¾; Ca or Sr=1½.

I. SODIUM AND CHLORID IONS.

That these ions are by no means devoid of actions is shown by the prompt death of cells placed in *pure isotonic solutions of NaCl.* They are, on the other hand, *absolutely essential* to most animals and to many plants. They *form the greater part of the electrolytes* existing in solution in the tissues and fluids of the vertebrates. (However, the mammalian blood corpuscles contain more K than Na.) Since a considerable quantity of these ions constantly leaves the body by the excretions, especially by the urine, they must be constantly replenished. Carnivorous animals obtain a sufficient supply in their *food.* But since K predominates over Na in the ash of plants, herbivora and animals feeding on a mixed diet require additional NaCl. This need has led to the *instinctive use of this salt:* in regions remote from deposits of this salt, ashes of plants which are rich in Na have been used by peoples as ignorant as the negroes of the interior of Africa.

The *excretion of NaCl keeps step,* within wide limits, with its ingestion; if the supply is stopped, the excretion falls to a very small amount, the tissues retaining almost their normal percentage. A small excretion continues, however, so that the tissues finally lose salts also. This leads to the phenomena of "*salt-hunger*" expressed particularly by metabolic disturbances, emaciation, etc. When the loss of salt has reached a certain degree, the animal dies.

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[1] All cathions stimulate the growth of plants in small doses, while larger doses hinder it.

[2] A summary of the excretion of salts is given by Heffter, 1903.

The chlorid excretion is also greatly diminished in some cases of nephritis; in fevers, particularly in pneumonia (where much salt is retained in the effusion); and during the rapid development of new tissue (cancer).

The mechanism by which the proportion of sodium chlorid in the blood and tissues is kept practically constant has been the subject of much investigation; but it is not understood. One theory (Forster, 1873) assumes that the greater quantity of the salt exists in the body in a form (perhaps as a *combination with the proteids*) in which it cannot pass through the living kidneys. This salt is therefor retained with great tenacity. Any excess over this, such as is normally present, is free and filters very readily into the urine. This theory is not quite satisfactory, but it agrees with the observation of Sollmann (1902) that the injection of those ions which are closely related to chlorid (viz., Br, I, NO_3, SCN) increases the chlorid percentage in the urine, whilst other ions do not have this effect: it may be assumed that the related ions can displace the chlorid from its proteid compound.

Cushny (1902), on the other hand, attributes the chlorid regulation to the absorbing mechanism of the tubules.

By means of these regulating mechanisms, an excess of these Na or Cl ions is eliminated very promptly, and could not produce any very large effect. But even when they are retained, these ions *produce only very small actions,* for the amounts normally present are so large that the artificial introduction of ordinary amounts will not increase their ratio to a considerable extent. Na and Cl are therefore the most indifferent of the ions, and their salts are used when the effects of other ions are to be tested. It is important to remember, however, that they are really very essential to the protoplasm, and that the absence of effects is due only to the fact that the variations which are introduced are relatively small.

II. THE POTASSIUM ION.

The *effects* of this consist in a depression of the central nervous system and of all kinds of muscle.

The *central nervous system* is paralyzed in its whole extent. The reflexes suffer, then the medulla. Depression of the respiratory center leads to asphyxial convulsions.

The *heart*[1] is stimulated by small, fatigued by medium, and paralyzed by large, doses. This is seen even in the nerve-free heart of the chick's embryo, and is therefore muscular. In mammals it develops sudden slowing and irregularity, and then stops, usually before the respiration (Fig. 91). The blood-pressure remains high during the convulsions, on account of the latter (for it falls in curarized animals).

The *skeletal muscles* are weakened and lose their irritability. Potassium in this way counteracts the effects of veratrin[2] (Fig. 70, page 325).

The symptoms are only seen in mammals if a potassium salt is injected directly into the circulation; they are very small if the salt is introduced hypodermically, and do not appear at all if it is taken by the stomach (except when it produces corrosion). The reason lies in the very rapid excretion.

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[1] Exercises 63 and 74.

[2] Exercise 45.

The blood corpuscles contain a considerable amount of K, so much that a fatal amount would be liberated by the dissolution of a fifth of the corpuscles. (The distribution of potassium within cells has been investigated by A. B. Macallum, 1905.)

Potassium is also in part responsible for the **toxicity of urine and the phenomena of uremia.** The toxic action which urine possesses when injected intravenously has been variously attributed to the leucomains, to toxins, etc., and at one time even to the urea. Various brilliant theories and methods of diagnosis were built upon the variations in this toxicity. It has, however, been shown that about 85% of the toxicity of the urine is due simply to its potassium salts. The symptoms are also precisely those of the latter. What causes the other 15% of the toxicity is at the present not known, but this may be connected with xanthin products. The increase of toxicity following muscular exercise favors this view.

If the undiluted urine is injected, its osmotic pressure also contributes to the toxicity. The acidity, volatile products, pigments, and urea have no effect. It is quite probable that the urine contains true toxins and other toxic products in disease, but no method has so far been devised for estimating the importance of these.

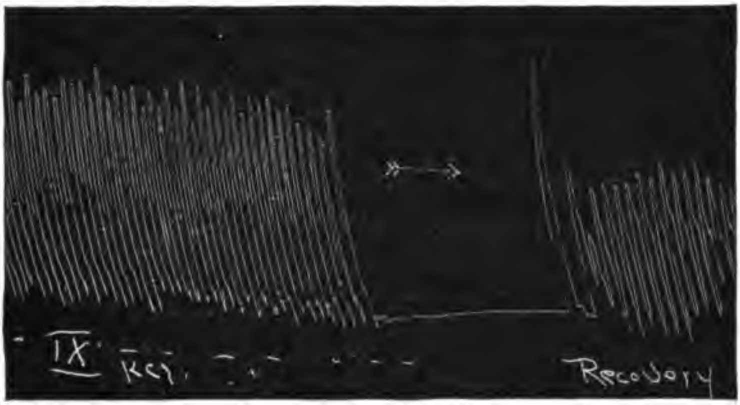

Fig. 91.—Cardiac effect of potassium, Langendorff preparation, dog. The heart stopped suddenly, after several doses had been injected without effect. The recovery occurs promptly when Locke's solution is readmitted.

The conditions are still more complicated in *uremia:* it is very probable that the retention of potassium and ammonium salts and the increased osmotic pressure of the blood contribute to the effects, but there seem to be other factors which are not understood. It is conceivable that an internal secretion comes into play; or it may be that the renal disease, or the underlying condition, gives rise to toxic products.

Therapeutic Uses.— The cardiac depressant action of the potassium ion can scarcely be utilized therapeutically, as it is not obtained by oral administration. The potassium salts are mainly used for their anions (*i. e.,* the acetate, bromid, chlorate, citrate, nitrate, etc.). They are contraindicated in renal insufficiency.

* *Potassii Chloridum,* KCl, readily soluble in water. *Dose:* 1 to 2 Gm. (15 to 30 grains). Not to be confused with the toxic chlorate!

III. THE LITHIUM ION.

The action of this cathion resembles potassium quite closely, but it is somewhat less toxic to the heart, and causes a vagus stimulation. These effects are only seen on intravenous injection. A most important difference from potassium consists in a *specific gastro-enteritis* which is produced even when the salts are given subcutaneously, or if the administration of small doses is continued for some time (1 Gm. of the carbonate in man). The action is local, the lithium being largely excreted by this channel. It is also excreted by the kidneys, but does not cause nephritis (Krumhoff, 1884; Good, 1902). Lithium was for some time used in therapeutics as a *solvent for uric acid,* in gout, and lithiasis. The solution is due to the comparatively great solubility of lithium urate. It has been shown, however, that this is true only in strong solutions, and does not exist in those which can be used in the body. The diuretic action of Li is no greater than with Na. The *employment of lithium is therefor quite irrational,* and in larger doses, dangerous.

MATERIA MEDICA.

Lithii Carbonas (U. S. P., B. P.).— Li_2CO_3. Soluble in 75 parts of water: *Dose:* 0.12 to 0.6 Gm. (2 to 10 grs.) (0.5 Gm. = 7½ grs., U. S. P.).

Lithii Citras (U. S. P., B. P.).— $Li_3C_6H_5O_7$. Soluble in 2 parts of water. *Dose* 0.3 to 1.0 Gm. (5 to 15 grs.) (0.5 Gm. = 7½ grs., U. S. P.).

Lithii Citras Effervescens (U. S. P., B. P.).— 5%. Completely soluble in water. *Dose:* 4 to 8 Gm. (1 to 2 drachms) (8 Gm. = 2 ʒ).

These lithium salts are insoluble in alcohol.

IV. RUBIDIUM AND CAESIUM.

These also resemble potassium. Rubidium iodid and bromid have been introduced into therapeutics, as it is claimed that they produce less iodism and bromism, although they are quite as soluble, and even more diffusible than the corresponding K salts. The doses are the same as those of the potassium salts.

V. AMMONIUM ION.

The ion action appears in the ammonium salts. The hydrate (ammonia) has an almost pure alkali action, and will be studied later. The ion action also appears in the *organic ammonium bases* — the amids and amins — in which the H of NH_4 has been replaced by organic radicles.

1. Actions.— (A) Peripheral Nerve Endings.— It will be remembered that the ammonium bases were discussed with the muscarin group, with which they shared the stimulation of the cardiac *vagus endings* and a *curare action* on striped muscles. These peripheral actions are much less conspicuous with the inorganic ammoniums, the stimulation of the central nervous system being much more prominent with the latter.

(B) In mammals, ammonium salts produce little effect when taken

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* Not official.

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by mouth. If they are injected *intravenously,*[1] they produec a pronounced stimulation of the *medulla and spinal cord,* followed in larger dose by depression of these centers. The *brain* is rather depressed from the start, so that the animals become somnolent. The *vasomotor, respiratory and vagus centers* are stimulated, and the blood-pressure is characterized by exaggeration of the respiratory waves (Fig. 92). The pulse is usually slowed, but may be quickened by the convulsions. Large doses depress the vasomotor-center and cardiac muscle.

Tetanus or *convulsions* appear rather late. Their seat is mainly in the spinal cord, and they resemble strychnin spasms to a very great extent. There is, however, coma.

(C) The ammonium ion has a very marked action in increasing the **secretions,** especially saliva, mucus, and sweat. The diaphoretic action is entirely central. The action upon saliva and mucus, however, is brought about by a number of factors: (1) By a *reflex stimulation* from mucous membranes due to a salt action, which is very large in the case of ammonium salts, as they penetrate very easily; or, in the case of ammonia water and ammonium carbonate, this is brought about by the *alkaline caustic action.* (2) *Direct stimulation of the secreting centers.* (3) *Local salt action* upon the secretory cells themselves. This is especially large since the ammonia salts are *excreted largely* into the mouth *by the saliva,* as also by the mucus,[2] mainly in the form of carbonate. In this way the local action is exerted twice, when the salt is applied and when it is excreted. (4) This excretion in the form of carbonate also tends to liquefy the mucus on account of the alkaline action.

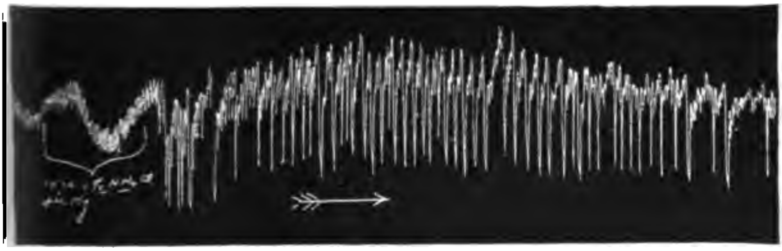

Fig. 92.— Ammonium chlorid, intravenous. Carotid pressure tracing, dog.

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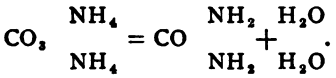
[1] Exercise 62.

[2] Ammonia is neither absorbed nor excreted by the lungs (Magnus 1902).

The *methyl ammoniums* formed by the substitution of the H atoms by CH_3 have actions closely resembling the above, differing mainly in a lesser action on the cardiac muscle (Formanek, 1900).

2. The **toxicology** of ammonia is really limited to ammonia water and ammonium carbonate, and these act not by their ion or salt action, but by their caustic alkaline action (Chap. XXVIII, A).

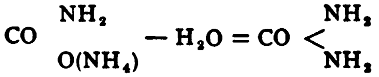
The ion action of other ammonium salts has no toxicologic importance, since they, like potassium, are absorbed too slowly and excreted too rapidly for the ion action to come into play at all. Further, the greater part of the ammonium ion is not excreted as such, but is rapidly *converted into urea,* according to the formula:



$$CO_3\begin{matrix}NH_4\\ \\ NH_4\end{matrix} = CO\begin{matrix}NH_2\\ \\ NH_2\end{matrix}+\begin{matrix}H_2O\\ \\ H_2O\end{matrix}.$$

Two molecules of water are split off from the ammonium carbonate and urea remains. This liberates the acid ion with which the NH_4 was combined: this will seize upon the free fixed alkali of the body, and lead to a diminished alkalinity of the serum. In this way any excess of ammonium introduced into the body is very soon eliminated, or at least ceases to act as ammonium.

It has been suggested, but without binding proof, that when the transformation of ammonia into urea is interfered with, an *autointoxication* may arise, with symptoms analogous to those produced by ammonium compounds. Some ammonia compound is probably a normal forerunner of urea. What this compound is, does not appear very plain, but one which has been suggested is ammonium carbaminate. The splitting-off of the H_2O from this yields urea:



$$CO\begin{matrix}NH_2\\ \\ O(NH_4)\end{matrix} - H_2O = CO < \begin{matrix}NH_2\\ \\ NH_2\end{matrix}$$

This transformation takes place to the largest extent in the liver as the result of the action of a ferment. When this organ does not functionate properly, the dehydration may not take place, and if there is an addition of H_2O instead, ammonium carbonate results. This may give rise to at least some of the symptoms which are noticed in cases of disease of the liver. The symptoms of uremia also resemble those of ammonium-poisoning. However, the ammonia is not increased in the blood, in either uremia or in acute yellow atrophy of the liver, but ammonium carbonate is found in the stomach and intestine. A considerable increase of the ammonia of the blood occurs in diabetic coma.

3. Therapeutic Uses.— The properties which have a therapeutic importance are the stimulating effect upon the central nervous system and the local action upon secretion. The stimulating effect upon the *central nervous system* may conceivably be a direct one, but, as has been pointed out, this must be very slight, for the ion does not remain in the body a sufficient length of time to exert any marked action. To attempt to modify the effect of an acid by giving it as an ammonium salt is scarcely scientific; for besides the quick excretion, the amount which could be given in this way is too small to have any influence.

Ammonia water and the carbonate have, however, a very marked stimulating effect upon the central nervous system, but this is *reflex* and is dependent only upon the local caustic action, enhanced by their volatility. This reflex stimulation — which is shown mainly on the medulla — can be produced by other means, but the inhalation of ammonia is one of the most efficient. The aromatic spirits of ammonia — 15 to 30 drops to the tumbler of water — is one of the best ways of producing these effects. In the form of smelling salts it is frequently used in fainting and in shock.

The stimulation of the *respiratory center* is useful in cough, asthma, edema of the lungs, pneumonia, or any case where the respiration is interfered with. The stimulation of the *sweat center* is useful as a diaphoretic measure, in colds, fever, etc. (see p. 282). For this purpose the Liquor Ammonii Acetatis is employed; this is probably absorbed somewhat more readily than other ammonium salts, so that there is perhaps some direct stimulation of the central nervous system.

The *local "expectorant" action* and the increased secretion of mucus have already been discussed and the manner in which this is produced pointed out; that is to say, by reflex irritation, possibly some direct stimulation of the central nervous system, by the salt action, and the excretion of ammonia in the form of ammonium carbonate. These probably suffice to explain the almost specific action upon the secretion of mucus. This is increased in amount and rendered thinner and less tenacious. When it is desired to affect the secretions low down in the trachea and bronchioles, the ammonium is very frequently administered in the form of inhalation of ammonium chlorid, produced in a finely divided state by bringing together the vapors of ammonia and hydrochloric acid. This can be inhaled to the finer divisions of the bronchi.

The somewhat stronger salt action of concentrated solutions of ammonium salts, leading to gastric irritation and vomiting, has been discussed with the emetics.

Ammonium chlorid has also been recommended as a specific in tropical dysentery. The number of observations upon its use is hardly sufficient to make a final decision as to its value. This could only be explained by a specific toxic action on the amœba coli.

4. Materia Medica of Ammonium Salts.

Ammonii Carbonas (U. S. P., B. P.)— (*Hartshorn, Baker's Ammonia, Sal Volatile.*) — $NH_4HCO_3.NH_4.NH_2CO_2$. Soluble in 4 parts water. *Dose:* 0.12 to 1.0 Gm. (2 to 15 grains), largely diluted (0.25 Gm. = 4 grs., U. S. P.).

Spiritus Ammoniæ Aromaticus (U. S. P., B. P.).—(*Aromatic Ammonia*):

Ammon. Carb.	3.4	*Dose:* 2 to 4 c.c. (½ to 1 drachms). Diluted with a glass of water. (2 c.c. = 30 ♏., U. S. P.).
Ammonia Water	9.0	
Aromatic Oils —		
Alcohol	70.0	
Water to	100.0	

Ammonii Chloridum (U. S. P., B. P.).— (*Sal Ammoniac.*)— NH_4Cl. Soluble in 2 parts water, 50 alcohol. *Dose:* 0.06 to 2 Gm. (1 to 30 grains) (0.5 Gm. = 7½ grs., U. S. P.). Best given in the form of:

Trochisci Ammonii Chloridi (U. S. P.).— Each 0.1 Gm. (1½ grains).

Liquor Ammonii Acetatis (U. S. P., B. P.).— (*Spiritus Mindereri.*) Made when required by neutralizing Ammonium Carbonate with Acetic Acid. *Dose:* 2 to 30 c. c. (½ to 8 drachms) (diaphoretic) (16 c. c. = 4 ʒ., U. S. P.).

VI. CALCIUM.

The action of calcium is directly depressant to all tissues and functions. When it is injected intravenously, it paralyzes the central nervous system, lowers the blood pressure, arrests diuresis and peristalsis, etc. This action, although very deleterious when excessive, seems to be the function of the calcium-ion in the body; for its removal (by oxalates, fluorids, or citrates) leads to strong stimulation and to death (Sabbatani, 1901 and 1902). This indicates the *vital necessity of calcium action.* Indeed, only a few of the lower fungi are able to live without it. It is also essential to the action of a number of ferments (rennet, fibrin ferment), but not to some others (pepsin).

In animals with a calcareous skeleton, calcium has another important function in bone formation.

A more gradual withdrawal of calcium from the body, by withholding it from the food, leads in animals to effects which closely simulate those of *rickets and osteomalacia.* There is, however, some difference: In calcium starvation,

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but little bone is formed, yet this contains the normal amount of calcium. In rachitis, the amount of bone is even excessive, but it is very poor in Ca. This paucity of calcium suggested its administration, particularly as calcium phosphate, in the treatment of these diseases. The results have been disappointing, as might have been deduced from theoretic considerations. The condition is somewhat similar to that existing in chlorosis, for except in the experimental disease, the cause of the disorder is never to be found in insufficient supply of calcium (or iron) salts, since the amount of these in the food is always more than enough to supply the demands of the organism. The real cause must be sought in the abnormal absorption or utilization of these ions.

The essential nature of this abnormal process is not at present known. In diseases in which there is an abnormal formation of acid in the blood — *e. g.*, diabetes — the excretion of calcium and magnesium is increased, but no such diminished alkalinity exists in rickets. Even if we assume the cause to be a deficient absorption, this could not be remedied by additional introduction of calcium, for it is of course extremely unlikely that calcium would be more easily absorbed from such inorganic salts as phosphates, than in the form in which it exists in the food.

Calcium phosphate has been recommended in *diabetes mellitus*, but has no effect, even in the mildest cases (Brüning, 1898). However, the injection of calcium salts arrests the glycosuria and polyuria induced by saline injection.

The use of calcium for *increasing the coagulability of the blood* was discussed in Chapter XXIII, A.

The depressant action of calcium suggests its use in *strychnin poisoning*, but Fischer (1904) found it ineffective. Zanda (1902) obtained better results by dural injection; but the effective dose was so large as to be itself dangerous. Deltjen (1904) has observed that small traces of calcium, strontium, barium, and magnesium lessen the solvent action of distilled water on cells.

The depressant actions of calcium are not observed when its salts are *taken by the mouth*, since these cannot be absorbed in sufficient amount. The small quantities which enter the body are excreted mainly through the intestine, in part also through the urine. This then becomes alkaline.

The **therapeutic uses** of calcium are practically confined to its hemostatic effect (see index). Calcium salts are frequently employed for their anions; the carbonate and phosphate act as mild alkalies.

MATERIA MEDICA.

Calcium Carbonate (*Chalk*).— $CaCO_3$. Insoluble in water. *Dose:* 0.5 to 4. Gm. (10 to 60 grs.) (1 Gm. = 15 grs., U. S. P.). Official as

Calcii Carbonas Præcipitatus (U. S. P., B. P.) and

Creta Præparata (U. S. P., B. P.).— *Prepared or Drop Chalk.*— Chalk freed from its coarser impurities by elutriation.

Used in the preparation of:

Pulvis Cretæ Compositus (U. S. P.).— Chalk, acacia, and sugar. *Dose:* 2 Gm. = 30 grs. (U. S. P.).

Pulvis Cretæ Aromaticus (B. P.).— Contains carminatives. *Dose:* 1 to 4 Gm. (15 to 60 grs.).

Pulvis Cretæ Aromaticus cum Opio (B. P.).— Contains 2½% of opium. *Dose:* 0.5 to 2.5 Gm. (7½ to 40 grs.).

Mistura Cretæ (U. S. P.).— 20% of compound chalk powder, with Cinnamon Water. *Dose:* 16 c. c. = 4ʒ (U. S. P.).

Liquor Calcis (U. S. P.).— *Lime Water.*— Made by slaking lime (*Calx,* U. S. P., B. P.), washing the slaked lime (*Calcii Hydras,* B. P.), and saturating Distilled Water with the product. Contains about 0.14% $Ca(OH)_2$. *Dose:* 4 to 30 c. c. (1 to 8ʒ.) (16 c. c. = 4ʒ., U. S. P.).

Syrupus Calcis (U. S. P.) [*Liquor Calcis Saccharatus,* B. P.].— A stronger solution of lime in syrup. *Dose:* 1.0 to 4.0 c. c. (15 to 60 ♏.) (2 c. c., = 30 ♏., U. S. P.).

Calcii Phosphas Præcipitatus (U. S. P.) [*Calcii Phosphas,* B..P.].— $Ca_3(PO_4)_2$. Almost insoluble. *Dose:* as for the carbonate.

Syrupus Calcii Lactophosphatis (U. S. P., B. P.).— Calcium carbonate, dissolved by a mixture of lactic and phosphoric acids, in a syrup flavored by Orange Flower Water. *Dose:* 8 c. c. = 2ʒ. (U. S. P.).

Calcii Chloridum (U. S. P., B. P.).— *Chloride of Calcium* (Not to be confused with Chlorinated Lime!).— $CaCl_2$, fused. Highly hygroscopic. *Dose:* 0.3 to 1.2 Gm. (5 to 20 grs.) (0.5 Gm. = 7½ grs., U. S. P.).

VII. STRONTIUM.

Strontium resembles barium in its actions, as also chemically. It stands, however, far behind in toxicity, being even less toxic than Ca. Like Ca, it hastens the coagulation of blood, although it is much weaker. This action is not shared by Ba or Mg. In dilute solutions only very small amounts are absorbed from the stomach; none from the intestine, since it is converted into phosphates, in which form it is also generally deposited in the bones. The urine contains only traces of strontium, even if it is given subcutaneously; the excretion occurring mainly by the intestine (Wood, 1898).

Strontium possesses no therapeutic indication. It may be useful to moderate the action of anions, since its salts must be decomposed before the anions can be absorbed.

Strontium bromid, iodid, and salicylate are official.

* *Strontii Lactas.*— Soluble in 4 parts water. *Dose:* 1 to 8 Gm. (¼ to 2 drachms).

VIII. BARIUM.

Unlike the other elements of its group, Ca and Sr, this element is very toxic. Its effects resemble those of the digitalis group: It produces the same action on the cardiac muscle; a strong vasoconstric-

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tion by direct stimulation of the arterial muscle (occurring therefor after apocodein, Dixon, 1903); strong stimulation of peristalsis, even on intravenous injection (Exercise 67); and a stimulation and later paralysis of the central nervous system. It also produces local irritation, and is inimical to the lower forms of life, such as yeast cells.

These actions are not utilized therapeutically (except in veterinary practice) on account of the toxicity. The excretion of barium occurs largely by the feces, as with Ca and Sr.

Its **local action** results in gastro-enteritis and some degree of corrosion, and fairly *large absorption*. It may, therefore, produce its **systemic actions** even when given by the mouth. The most conspicuous of these are upon the circulation: a slowing of the heart (digitalis action), and a rise of blood-pressure (constriction of arterioles). The pulse is, therefore, small, hard, and slow. Large doses paralyze the cardiac muscle.

When given in very dilute solutions the amount absorbed is very small, and is then *deposited in the bones*. The *fatal dose* of barium salts is given as 3 to 15 grains. The chemic antidotes are sulphates (Glauber's salt), which act by forming the insoluble barium sulphate.

IX. MAGNESIUM.

(The therapeutic importance of the Mg ion is confined to its cathartic action (see page 544). If it is given by the alimentary canal, very little is absorbed and it has no further effects. It is, however, an essential constituent of protoplasm, being necessary especially to the extranuclear portion of the cells. If it is injected directly into the circulation it produces effects which resemble those of potassium, especially a prompt paralysis of the heart. If this is not acutely fatal, complete recovery occurs very quickly.

The administration of soluble magnesium salts increases the elimination of calcium, and thus lessens the calcium deposition in young animals (Malcolm, 1905).

X. BROMIDS.

The *experimental data* in regard to this ion are as yet very unsatisfactory. The doses which can be introduced do not produce any decisive phenomena in animals. The most conspicuous effects are observed in epilepsy. But here the KBr is far more efficient than NaBr; and since other K salts also exert a similar action, some authors have regarded the Br ion as entirely inactive. This does not do justice to the evidence — for these other K salts are much less efficient than the bromid, and NaBr is also effective. The K aids, however, and KBr is always preferred.

In any case the action of the Br ion is small, and consists in a depression, rather than in abolition, of function. The action is studied in much the best manner in man, because slight changes in the central nervous system are extremely difficult to observe in animals. In man it leads to depression of mental activity in general, but certain kinds are much more readily influenced than others. These differences have not been sufficiently studied. The defect seems to be in appreciation rather than in perception; just as in the case of morphin, it seems that the stimuli reach the brain, but are not appreciated in the ordinary manner. But the power of observation and attention are not interfered with in moderate doses. In the case of reflexes it seems to be the *connecting link* between the central cells which suffers, so that the main effect is not upon the primary reflex, but upon other reflexes which may arise from this. So also a stimulation of the motor areas which, under the conditions of the experiment, gives rise to general epileptiform convulsions, will, after the administration of a bromid, be confined to the area directly stimulated. If a bromid is administered to animals under strychnin, the effect of stimulation does not have much tendency to spread, whilst the primary reflex, say the patellar, will still be exaggerated. Although the main interference is with the spreading of the impulse to other parts, the direct *reflexes* are also diminished. This was utilized before the days of local anesthetics, for instance, in the examination of the throat.

Large doses of potassium bromid may have an action upon the heart, depending entirely upon the potassium ion.

2. If the administration of bromids is continued for a considerable length of time, there results a series of symptoms grouped under the name "**bromism.**" These depend on a local irritant action, which finds expression in gastritis, in acne, in coryza, etc. It is due partly to the salt action of the bromin salt, also probably in part to a decomposition of the bromid, with liberation of bromic acid and bromin, by the free acids existing in these situations: in the stomach, hydrochloric acid; in the mouth, large quantities of carbonic acid; in the skin, especially the acid secretions of the sebaceous glands. It is favored by insufficiency of the kidney. It is more easily produced in old age.

3. The **excretion** of the bromid begins very quickly, but lasts for a very long time, traces appearing in the urine for over sixty-five days. The main amount is found in the blood, and next to this in the brain and kidneys; the liver, bile, and spleen are free from it. This slow excretion lends support to the theory that the bromin enters into combinations in the body, and it is very likely that it may to some extent take the place of the chlorin in its protoplasmic compounds. The excretion of chlorids is increased. The administration of NaCl quickens the excretion of the Br, and lessens the symptoms of bromism, but also the other effects.

If the same dose of bromid is taken daily, a condition of equillibrium becomes established in about two or three weeks, so that as much is excreted as is taken in; this is disturbed whenever the dosage is altered. Chlorids and iodids behave in the same manner.

The phosphates of the urine are somewhat diminished, the N increased, but the metabolic action is not large (Chittenden, 1884).

The bromid action can only be obtained from fairly large doses, is always rather small, and is not usually seen until the administration has been continued for some time.

No effect can be expected from the bromin in salts which are used in small doses — *e. g.,* bromid of quinin, of arsenic, etc. In these it can only be useful by influencing the solubility or dissociability of the compound.

The **effects of the continued administration** of bromids consist in an exaggeration of the effects observed after a single dose. There is dullness, bad memory, sometimes aphasia; and, in general, lowered activity of the central nervous system. Partly on account of this, partly on account of the gastritis and general irritant action, there is a lowered resistance on the part of the patient. All these symptoms seem to disappear quite quickly on the withdrawal of the drug, persisting only a little longer than the bromin remains in the body.

4. Therapeutics.— Bromids are used mainly against epilepsy. They were introduced for this purpose in 1853. They do not seem to be efficient in all cases, probably because epilepsy has different causes. The successful cases amount to something like 90% in idiopathic epilepsy.[1] Large doses must be employed and continued for some time. The potassium bromid is the more efficient salt. On the other hand, the calcium or strontium bromids are less irritant to the stomach, since they must be decomposed before being absorbed, and the bromid ion is therefore liberated more slowly. The attacks of epilepsy usually return as soon as the remedy is removed. In some few cases, however, a permanent effect seems to have been obtained. It is possible that this cure was not due to the bromin, but was spontaneous.[1]

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[1] Binz gives the following compilation:
Permanent cures, 40%.
Total abolition as long as drug is continued, 12%.
Diminished number and violence of attacks, 83%.
No influence, 2½%.
Number of attacks increased, 2½%.

It has also been attempted to employ bromid against other diseases which rest upon a heightened irritability of the central nervous system — for instance, *chorea and tetanus.* The results have been variable; sometimes it has been efficient, and at other times not. It is useful, however, in all cases of *overaction of the brain* — worry, etc.— and all the conditions which arise from these — *e. g.,* insomnia and nervousness. It is of no value in pain. The depression which it produces is rather lasting, so that it is not indicated as an ordinary hypnotic. It is useful in all cases where there is an *exaggeration of reflexes,* such, for instance, as some cases of cough; in *incontinence of urine* if this results from overaction of the detrusor center. It may be useful in *reflex vomiting.* It has been recommended in both seasickness and pregnancy; the results have been variable. It is useful in *pertussis* (1 Gm. per day for a child one year old). Large doses are often curative in acute mania — as much as 100 Gm. may be given, distributed over three days.

As to the manner of administration, the bromids should always be largely diluted, and are best flavored with peppermint or wintergreen.

It is claimed by some clinicians that the sodium and ammonium bromids, or mixtures of several bromids, are better tolerated by the stomach. Erlenmeyer recommends the proportion KBr : NaBr : NH_4Br as 2 : 2 : 1.

5. **Materia Medica.**— The bromids are readily soluble in water, fairly soluble in alcohol. They are given in *doses* of 0.3 to 4. Gm. (5 to 60 grs.); for children, about 0.05 Gm. (1 gr.) per year. Bromids are incompatible with strychnin.

	One part is soluble in water:	alcohol:
Ammonii Bromidum (U. S. P.).— NH_4Br	1.2	12.5
Calcii Bromidum (U. S. P.).— $CaBr_2$	0.5	1.
Lithii Bromidum (U. S. P.).— LiBr	0.6	very sol.
Potassii Bromidum (U. S. P., B. P.).— KBr	1.5	180.
Sodii Bromidum (U. S. P., B. P.).— NaBr	1.7	12.5
Strontii Bromidum (U. S. P.).— $SrBr_2 + 6H_2O$	1.0	readily sol.
Zinci Bromidum (U. S. P.).— $ZnBr_2$	readily sol.	readily sol.

Dose: 0.125 Gm. = 2 grs.

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[1] The treatment of Epilepsy: Besides the bromids, the following drugs have been used empirically: Opium, Valerian, Belladonna, Zinc Oxid, Chloral, Adonis Vernalis, Solanum Carolinense, salicylates and antipyretics. It is very difficult to form an estimate of their value, since epilepsy is temporarily benefited by almost any placebo. These drugs can only be recommended when bromids have failed or are for any reason badly borne. No treatment will be successful except it be joined with a careful regulation of diet and general hygiene, excesses of all kinds being strictly proscribed.

The inhalation of Amyl Nitrite is sometimes useful during the attack.

* *Pulvis Potassis Bromidi Effervescens* (N. F.).— A heaped teaspoonful contains 0.6 Gm. (10 grains).

* *Pulvis Potassii Bromidi Effervescens cum Caffeina* (N. F.).— Contains, in addition, 0.06 Gm. (1 grain) Caffein.

* *Elixir Potassii Bromidi* (N. F.).— 4 c.c. (1 drachm) = 0.6 Gm. (10 grains) KBr.

Acidum Hydrobromicum Dilutum (U. S. P., B. P.).— 10%. *Dose:* 5 to 10 c.c. (1 to 2½ drachms), diluted (4 c.c. = 1 ʒ, U. S. P.).

* *Bromipin,* a combination of 10% of bromin and oil of sesame, is said to be more readily absorbed, to be less irritant, and less liable to produce bromism. *Dose:* 4 to 15 c.c. (1 to 3½ drachms) per day.

XI. IODID ION.

Our knowledge of the actions of the iodid ion is derived from clinical, rather than from experimental, data.

The iodids are *specific in tertiary syphilis* and its sequels.[1] They also affect chronic rheumatism and asthma. They lead to the resolution of various pathologic formations, especially those involving connective tissue. They also produce obscure changes in metabolism, leading to marasmus and cachexia. The excretion of N is increased, but it occurs in less completely oxidized form. The same is true of sulphur. Iodin itself has a very similar action.

These phenomena can all be reduced to alterations in metabolism, which, as usual, influence most profoundly the less vigorous and less stable pathologic connective tissue formations.

Iodids on **intravenous injection** exert a quite characteristic action on the cardiac **vagus endings,** paralyzing them after the manner of atropin. They also lower the excitability of the depressor, so that stimulation of its trunk does not lower the pressure in the normal manner. In the frog, they cause rigor of the skeletal muscle. In rabbits they produce death through pulmonary edema with pleural effusions. The latter phenomena are probably due to the irritant action of liberated iodin. The statements regarding central actions are contradictory, and probably untrustworthy (Barbera, 1900; Jodlbauer, 1902; Heinz, 1898).

1. Explanation of Action.— No complete and unassailable explanation of the metabolic effects of iodids is possible with our present knowledge. There are, however, some very suggestive facts: The absence of any circulatory or nervous actions shows that the effects of the iodids must be exerted *directly on the cells.* It is easy to understand that the salt and ion actions of iodids on the protoplasm must be very large and profound: The iodid ion is very *diffusible,* and penetrates readily into most cells. It is an *absolutely foreign ion* to the body. The *potassium ion,* in combination with which it is usually administered, is also practically a foreign ion, so that the KI is especially active. On the other hand, the *close relation of the iodid ion to the chlorid ion leads* to the ready displacement of the latter from its combinations, as is shown by the fact that the excretion of the chlorids is greatly increased. This, and the slow excretion of the iodid support the view that it enters into loose *ion-compounds* with the proteids, and it is very reasonable to suppose that the properties of these compounds differ from those of the corresponding chlorid compounds. Indeed, Pauli (1903) has shown that the effects of iodids, and the allied sulfocyanids, on the *viscosity of colloids* is especially large, as these render proteid solutions more fluid.

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* Not official.

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[1] They were introduced for this purpose about the middle of the present century.

The iodids are furthermore very readily decomposed, under the conditions of the body, with the *production of hydriodic acid and free iodin.* These may *enter directly into the proteid molecules,* producing compounds with new properties. Iodothyrin is the most important of the organic iodin compounds in mammals; but according to Justus (1902) organic iodin is present in all cell nuclei.

Bromids or sulfocyanids cannot replace this iodin; nor can bromin be found in the thyroid gland when bromids have been administered.

All these factors are, to a variable degree, concerned in the action of the iodid ion on metabolism; but it is quite conceivable that other factors, which are not at present appreciated, may play a prominent rôle.

The *excretion* of iodids[1] occurs mainly by the urine and begins very early. The excretion begins within ten or twenty minutes and reaches its maximum in two hours; it persists, however, for a considerable time, with doses of 0.5 Gm. for 40 hours, with larger doses for 20 days. The excretion can be hastened by administering chlorid of nitrates, but not by diuresis. Considerable iodid is also excreted by the saliva and mucus (tears, stomach, cerebrospinal fluids, etc.), but is mostly reabsorbed. Sweat contains only traces (Kellermann, 1905).

2. Iodism.— The liberation of free iodin and hydriodic acid, which are both strong irritants, may give rise to very unpleasant side-effects resembling in a general way those which were described as bromism — gastritis, various skin diseases, coryza, increased bronchial secretion, parotitis, etc. The iodids are very weak compounds and are decomposed even by carbonic acid and nitrites. Since these are most abundant in the respiratory organs, these show a pronounced local action. The extent of the local manifestations of iodism varies greatly in different individuals, or in the same individual at different times; this may perhaps be explained by a different degree of acidity. Iodism can be prevented very largely by the administration of alkalies or chlorids.

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[1] Exercises 13 and 26.

Some clinical observers claim that large doses are often better borne than small; and that syphilitic patients are less subject to iodism than others. The statements need confirmation.

4. Therapeutics.— 1. Third Stage of Syphilis: The continued administration of iodids in this stage removes all the symptoms in a specific manner, arrests the progress of the disorder, and repairs the existing lesions.

It is impossible to say at present whether the iodids exert a specific action on the syphilis organism, if such exists, whether their effect is due to an ion action on metabolism, or whether it is simply a general salt action, the breaking down of pathologic new-formation. The iodids alone seem to have no action in the first and second stages of syphilis. But in the latter they are often useful in combination with mercury.

It makes no difference in this case whether one gives mercuric chlorid and potassium iodid, or mercuric iodid; for the latter will be decomposed into mercuric chlorid, and its iodin will form sodium iodid.

The iodin also seems to aid in the removal of mercury which has been accumulated in the body during the first and second stages.

It seems to be similarly useful in the removal of lead in chronic lead-poisoning. It acts, perhaps, by stimulating the general activity of the cells, but the subject is very little understood.

2. Its action in **chronic rheumatism** presents the same problems, and it cannot be decided whether it acts by destroying the organisms, or by changing their products, by removing the lesions, or by altering metabolism.

3. Similar questions arise in connection with its benefits in many cases of **asthma,** It could be conceived as irritating the mucous membrane; as liquefying the mucus; as altering the vascularity; as paralyzing the vagus endings, etc. These factors may all enter into its action, but nothing can be definitely affirmed.

4. Iodids cause a **reabsorption of hyperplastic fibrous tissue,** and will therefore reduce chronic inflammatory swellings. They may cure fibrous goiters. They are also of pronounced benefit in arteriosclerosis, which they may cure entirely if it is not too far advanced. They do this by

causing the disappearance of the increased fibrous tissue. Their action on tuberculosis and chronic pneumonias is partly referable to this. They are also recommended in actinomycosis.

5. They are very useful as **expectorants,** through their deep and lasting salt action, and by liquefying the mucus.

It has been claimed that they diminish the secretion of milk, but the statement does not rest on secure evidence.

5. Materia Medica.— The iodids should be administered in gradually increasing doses, in such a way as to cause the minimum gastric derangement. The KI produces the maximum effect. It is claimed that SrI_2 causes the least side-actions. Their *dose* is 0.3 to 4 Gm. (5 to 60 grains).

In syphilis, the treatment may be started with 1.5 Gm. three times a day (two hours after meals); increasing the dose by 0.3 Gm. every second day. Iodids are readily soluble in water, fairly in alcohol. *They should never be used with calomel.* They are also incompatible with strychnin. Salts which have become yellow through the liberation of iodin should not be dispensed.

	One part is soluble in water:	alcohol:
Ammonii Iodidum (U. S. P.).— NH_4I	0.6	9.
Potassii Iodidum (U. S. P., B. P.).— KI	0.7	12.
Sodii Iodidum (U. S. P., B. P.).—NaI	0.5	3.
Strontii Iodidum (U. S. P.).— $SrI_2 + 6H_2O$	0.5	sol.
Zinci Iodidum (U. S. P.).— ZnI_2	readily	readily

Dose: 0.065 Gm. = 1 gr.

**Solutio Potassii Iodidi* 1 : 1 (1 ♏. = 1 gr.).—Dissolve 1 ℥ in 5½ ʒ of water, and make up to 1 fl ℥.

Unguentum Potassii Iodidi (U. S. P.).— 10% in benzoinated lard (irrational).

Acidum Hydriodicum Dilutum (U. S. P.).— 10%. *Dose:* 0.5 c. c. = 8 ♏. (U. S. P.).

Syrupus Acidi Hydriodici (U. S. P.).— 1%. *Dose:* 4 c. c. = 1 ʒ. (U. S. P.).

**Iodipin* is a compound similar to Bromipin (see p. —), and contains 10% of iodin. The same advantages are claimed for it. *Dose:* 4 to 15 c. c. (1 to 4 drachms) by mouth, or 10 c. c. of 25% suspension injected into the gluteal muscles.

XII. SULFOCYANID ION.

This ion does not show any cyanid action. It influences the aggregation of colloids in the same way as the iodid ion, being even somewhat more solvent. This analogy suggested a therapeutic trial. In the as yet rather limited number of cases in which it has been tested, it was found to affect neuroses, arteriosclerosis, and syphilis in a manner analogous to the iodids, being even somewhat stronger (Pauli, 1903). It also hastened the elimination of metals — perhaps by rendering the metal-proteid compounds more soluble. It resembles the iodids further in producing coryza, acne, and other symptoms of iodism. A conspicuous difference from iodids lies in the fact, that it does not act on the thyroid gland. It was used as the *sodium sulfocyanid,* in the maximal dose of 1 Gm. (15 grains) per day. This salt is quite soluble in water. The potassium salt could probably be used in the same dose.

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* Not official.

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XIII. FLUORID ION.

Sodium fluorid is a general protoplasmic poison. It has a strong *local irritant action,* a 2% solution being corrosive to mucous membranes. The *systemic action* resembles that of the oxalates and is probably produced in the same manner, by the formation of insoluble calcium salts.

In the *frog,* it produces fibrillary contraction of the muscles. These disappear on section of the nerve. Larger doses produce rigor. The systemic effects are dyspnea, loss of reflexes, stoppage of respiration, cardiac standstill. In *mammals* it causes salivation, gastro-enteritis, dyspnea, muscular weakness and tremors, epileptic convulsions, fall of arterial pressure, and stoppage of respiration and heart. Rigor sets in quickly. The abdominal organs are congested. The intestinal epithelium is destroyed (even when the poison is introduced by other channels), whilst the cilia of the respiratory epithelium may still be moving (Siegfried, 1901).

When fluorids are given in small amounts, greatly diluted, they are absorbed and *deposited* for the most part *in the bones.*

The bones become unusually hard, white, and brittle, and contain small crystals, presumably CaF_2. A small amount of the latter is normally contained in the bones and teeth, but the percentage (0.02 - 0.05) is so small that it cannot be regarded as essential (Jodlbauer, 1901).

The fluorids are quite markedly *antiseptic.* In the proportion of 1 : 200 they prevent completely the development of bacteria, and are sometimes used for this purpose. They have no important therapeutic application, and small toxicologic importance.

* *Sodii Fluoridum* (Sodium fluorid), NaF.— Soluble in 25 parts of water. Used externally as antiseptic. For dressings, 0.5 to 10 : 1000; injections, 0.25 to 1 : 1,000; against fermentation in food, 10 to 15 mg. per Liter. 0.25 Gm. have produced dangerous symptoms in man.

* *Hydrofluoric Acid* is a very violent volatile caustic. The burns suppurate, and heal very slowly.

XIV. THE NITRATE ION (NO_3).

1. Action.— In addition to an extensive salt action, this appears to produce a more specific irritation, which must be referred to the ion. The salt action is explained by its ready penetration, and by its being entirely foreign to the animal body. The specific irritation is exerted mainly on mucous membranes, and results in gastritis at the place of entrance; in diuresis, or with large doses nephritis, at the place of exit.

Smaller doses, long continued, cause a hemorrhagic tendency, edema, and fatty heart (Fackelmann, 1898).

The nitrates are also reduced to a large extent in the body. A certain proportion is excreted as nitrite. This reduction takes place so slowly, in the case of the inorganic nitrates, that no nitrite action can ordinarily be seen; but very large doses may cause methemoglobin formation (Binz and Gerlinger, 1901).

The **excretion** of nitrates presents the same peculiarities as that of the chlorids, bromids, and iodids.

In the case of *potassium nitrate,* considerable of the effect must be attributed to the potassium, and this salt is usually employed when the potassium action is desired. This is due to the fact that the nitrate ion increases the rapidity of the absorption of its cathion. Potassium nitrate has therefore a *twofold action:*

2. Therapeutics.— The *nitrate ion* is used for diuresis. For this purpose 4 Gm. of the KNO_3 are taken in a large quantity of water. If the latter is carbonated, the absorption will be quickened, and the gastric irritation proportionately lessened.

The *potassium ion* may be used to depress the heart, having much the same indications as aconite — sthenic fevers, such as an acute articular rheumatism, etc.

3. Materia Medica:

Potassii Nitras (U. S. P., B. P.) (*Niter, Saltpeter*), KNO_3. Soluble in 3.6 water, very sparingly in alcohol. *Dose:* 0.3 to 1.2 Gm. (5 to 20 grains), largely diluted (0.5 Gm. = 7½ grains, U. S. P.).

Sodii Nitras (U. S. P.).— (Chili Saltpeter).— $NaNO_3$.— Sol. in 1.1 water, 100 alc. *Dose:* as the preceding.

XV. TOXICOLOGY OF NEUTRAL SALTS OF ALKALIES.

The irritant action of KNO_3 is so violent, if the salt is taken in concentrated form or in large doses, that it has a considerable toxicologic importance. The same phenomena are produced by all other neutral salts which do not possess a specific toxicity, so that the following description will be generally applicable.

Since the capacity for the excretion of these salts is greater than the capacity for their absorption, they do not usually develop their ion action when taken by the mouth. However, if introduced in strong solution they may cause necrosis of the lining membranes, and will then enter the circulation more rapidly, and produce the ion symptoms described under the several headings. Ordinarily their action is a purely local one, proportional to their concentration and to the time during which they remain in contact. The latter again is proportional to their quantity. Since the concentration is necessarily greatest at the points where they enter and leave the body, the irritation is most manifest in the alimentary canal and in the kidneys, producing gastritis, enteritis, and nephritis. The phenomena are the same as with other irritant poisons (see Chap. XXVIII, A). They consist in great abdominal pain, vomiting, frequently bloody stools; irregular pulse, convulsions, and collapse; suppression of urine, or that passed is albuminous and often bloody. The gastro-enteritis may be so violent as to lead to an early fatal ending. Of the salts so far studied, the potassium nitrate is by far the most violent; 30 Gm. (1 ℥) may be fatal if taken in concentrated form.

The *treatment* would consist first in dilution, since they act only by virtue of their concentration. Large quantities of water should be drunk and the stomach washed. Demulcents — milk, egg white, acacia — are also useful. The symptoms should be met as they arise.

XVI. THE CHLORATE ION.

The chlorates display some peculiar ion actions:

They are strong oxidizers chemically, but do not exert this action in the body.

When the chlorates are added to blood, either inside or outside the body, they effect the *formation of methemoglobin*. The chlorate ion is not used up in this process, so that it may convert an indefinite amount of hemoglobin. They differ in this respect from the nitrites (see index), and their action is in consequence more violent and more prolonged. They may in this way produce an actual asphyxia.

The blood of different animals shows a different degree of susceptibilty for this methemoglobin formation. These differences are common with all poisons acting on the blood, especially as between carnivorous and herbivorous animals. The cause is not understood, but is perhaps connected with differences in the alkalinity of the body. The conversion occurs fairly readily *intra vitam* in man, dog, and cat, whilst rabbits and guinea-pigs are almost immune. But in the test-tube chlorates convert rabbit's blood, although more slowly than dog's. The action is much slower outside of the body, often requiring several hours.

Iodates and Bromates have a similar action on hemoglobin (Heinz, 1898).

In addition to this formation of methemoglobin, the chlorates break up the *blood-corpuscles.* This was formerly supposed to produce dangerous embolism, but less importance is attached to it at present. But the proteids, etc., which are liberated by the destruction of the corpuscles are extremely irritant to the kidneys and produce a very marked interstitial *nephritis,* with the usual phenomena — proteids in the urine, casts, sometimes hemoglobin compounds. Possibly the chlorate ion itself irritates the kidneys.

The chlorates have also a *disinfecting and local stimulant action,* which seems to be rather stronger than would be accounted for by their salt properties, and would therefore appear to be a specific ion action.

Excretion.— Chlorates are excreted mainly by the urine, but partly also by the saliva. The urinary excretion begins promptly and is completed within 48 hours, all the chlorate being recovered. A great deal of this, however, is reduced to chlorid after the urine is voided. It is doubtful whether this reduction occurs in the body. *Bromates,* however, are partly reduced in the tissues, and iodates intensively.

The **toxicology** of potassium chlorate is fairly important. Poisoning very frequently takes place accidentally, either by an overdose, since the laity does not generally regard it as a toxic substance; or by the swallowing of some of the solution given for gargling.

The **symptoms** are those of a *gastro-enteritis,* as just described (p. 575). After its absorption, it produces symptoms due to the methemoglobin formation and destruction of corpuscles; *i. e.,* peculiar *cyanosis, nephritis,* hematuria, blood casts, possibly suppression of urine. Icterus is also common. If the action on the kidney is still stronger, uremic symptoms — coma and convulsions — may result. The course of poisoning may be very rapid. Death has taken place in two and a half hours. Usually, however, it does not occur for several days.

The **treatment** would be the same as for other irritant salts.

Therapeutics.— The local disinfectant and stimulant action to mucous membranes is alone important, and is extensively utilized as a gargle in sore throat and stomatitis. The patient should be cautioned against swallowing the solution. There would seem to be little indication for its internal use. and the popular tablets are to be condemned.

MATERIA MEDICA.

Potassii Chloras (U. S. P., B. P.), $KClO_3$.— Soluble in 16 water. Insoluble in absolute alcohol. *Dose:* 0.2 to 1.2 Gm. (3 to 20 grains) (0.25 Gm. = 4 grs. U. S. P.). As a gargle, 1% to 5% solution.

Trochisci Potassii Chloratis (U. S. P.).— Each contains 0.15 Gm. (2½ grains).

Trochiscus Potassii Chloratis (B. P.).— Each contains 0.2 Gm. (3 grains).

Sodii Chloras (U. S. P.).— $NaClO_3$. Sol. in 1 water, 100 alc. *Dose:* 0.25 Gm. = 4 grs. U. S. P.

The chlorates *explode* when triturated with organic matter.

XVII. THE PERMANGANATE ION.

This is so readily decomposed into O and MnO_2 in contact with organic matter, that its action can never be anything but local. It is an irritant and disinfectant. Taken by the mouth in large dose it may cause death by gastroenteritis.

The **Potassium Permanganate** (U. S. P., B. P.) ($KMnO_4$) is the only salt used. Soluble in 15 water. Decomposed by alcohol and all organic matter; explosive. *Dose:* 0.065 Gm. = 1 gr. U. S. P. It may be taken in ⅓% solution as antidote to organic poisons, HCN, and phosphorus. Its main use is as an antiseptic. It is so readily destroyed and so expensive that its usefulness is limited. 1 : 2,000 to 1 : 500 solution may be used as injection in dysentery, in urethritis, or as mouth-wash. A saturated solution (1 : 16) may be used for the hands, the color being removed by a solution of oxalic acid. The MnO_2 into which it is decomposed is employed against chlorosis. For this purpose the *dose* is 0.03 to 0.1 Gm.

XVIII. ACETATES, CITRATES AND TARTRATES.

The acetates and tartrates have no peculiar ion action. They act just like other neutral salts; but, like the alkali salts of most organic acids, they are decomposed in the body with the formation of carbonates: $HC_2H_3O_2 + O_2 = 2CO_2 + 2H_2O$; so that they exert an alkaline action after their absorption. This alkali action is of special importance on account of the profuse diuresis which results from it. The citrates and tartrates are not readily absorbed, and are therefore *cathartic.*

The addition of ***sodium citrate*** to calcium salts produces a compound (containing three molecules of the former to one of Ca) in which the *Ca ion is inactive:* it is not actually precipitated, but does not give the Ca reactions. A similar result occurs ***if citrates are injected directly into the circulation.*** This inactivation of the Ca leads to effects identical with those of removal of Ca by other means, as by oxalates or fluorids; stimulation of the central nervous system, with convulsions, followed by paralysis. These effects are never seen when citrates are given by mouth, since the slow absorption permits complete decomposition. Citrates also *retard the coagulation of blood and casein,* by inactivation of the Ca, in the same way as oxalates. *Tartrates* have similar, but weaker, action (Sabbatani, 1901; v. Vietinghoff-Scheel, 1902).

MATERIA MEDICA.

The *dose* of the salts is 0.3 to 4 Gm. (5 to 60 grains) (1 Gm. = 15 grs. U. S. P.).

The salts are very soluble in water. The potassium salts are hygroscopic, and should not be dispensed in powders! The sodium salts, on the other hand, effloresce.

1 part is soluble in	Water:	Alcohol:
Potassii Acetas (U. S. P., B. P.).— $KC_2H_3O_2$	0.4	2.
Sodii Acetas (U. S. P.).— $NaC_2H_3O_2 + 3H_2O$	1.	23.
Potassii Citras (U. S. P., B. P.).— $K_3C_6H_5O_7 + H_2O$	0.5	spar. sol.
Sodii Citras (U.S. P.).— $2Na_3C_6H_5O_7 + 11H_2O$	1.1	" "

Liquor Potassii Citratis (U. S. P.).— Effervescent; 8%. *Dose:* 16 c. c. = 43 (U. S. P.).

Tartrates, see index.

XIX. OXALATE ION.

Oxalic acid is quite a strong organic acid, and exhibits the ordinary acid actions. The oxalates act as soluble salts. In addition to this, however, they show an effect which must be referred to the oxalate ion. This consists of a specific **toxicity to all protoplasm.** The phenomena resemble superficially those produced by HCN. The action is probably explained by the fact that the calcium is rendered insoluble.

In accordance with this theory, it is found that oxalates are not toxic to a few lower fungi which do not contain calcium. They are toxic to most plants, but certain species contain soluble oxalates. In algæ the main histologic changes are seen in the portions richest in calcium — nucleus and chlorophyll. Oxalic acid is probably a constant product of metabolism, and possibly one of the functions of calcium is to render it harmless.

If dilute solutions of oxalates are applied directly to skeletal muscle, they cause rhythmic contractions. Lessening the proportion of Ca by any other means has the same effect. Larger doses of oxalates depress the excitability and force of the skeletal and cardiac muscles.

If oxalates are **injected into the circulation** they affect first the *central nervous system* in its whole extent, from mental functions to reflexes, producing at first stimulation, with convulsions, and then *paralysis,* the latter being the more conspicuous with large doses.

The medullary centers are especially affected. In consequence of the *asphyxia* produced in this manner they cause glycosuria, and possibly through the same cause indicanuria. *Death* occurs from respiratory paralysis, excepting when the poison is injected directly into the circulation, in which case it may paralyze the cardiac muscle (v. Vietinghoff-Scheel, 1901).

Taken by the mouth, the oxalates are *readily absorbed,* and poisoning is not at all infrequent from confusion with other salts.

The **symptoms** are: first, those of a local caustic, especially when

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the acid was used; then those of collapse, the latter possibly preceded by convulsions. The pulse is very small and weak.

Almost the entire quantity is *excreted,* unchanged, by the urine (92% to 95% after hypodermic injections) in the form of calcium oxalate. This is almost insoluble and forms envelope-shaped crystals, which are diagnostic of oxalate-poisoning. The crystals may be excreted in such great amounts as to block the urinary tubules, and may thereby possibly lead to *nephritis,* or retention of urine and uremia. Calcium oxalate, in rod-shaped crystals, may be found in all the organs, but it may be absent from these in very acute poisoning (Mürset, 1885).

Metabolism is markedly depressed in oxalate poisoning, especially the production of carbonic acid. The respiratory quotient falls (Corley, 1902).

Death by oxalic acid and oxalates occurs very rapidly, much more quickly than by any other caustic substance. This is of diagnostic importance. (In one case death took place in ten minutes.) The *fatal dose* will vary with the concentration. The smallest recorded amount is 5 grams.

The chemic *antidote* would be calcium in any shape, chalk, lime-water, etc., (Husemann). Liberal quantities of water should be given to prevent the deposition of crystals in the kidneys.

Oxalates have no therapeutic importance. They may occur in rather large quantity in some articles of food,—*e. g.,* spinach,—but not in such amounts as to be dangerous.

**Acidum Oxalicum,* $C_2O_4H_2$; colorless crystals, easily soluble in water.

**Acid potassium oxalate,* KHC_2O_4.

XX. BORIC ACID AND BORAX.

These combine a very fair **antiseptic power** with a low toxicity to higher animals. They are also less irritant than most other antiseptics. Boric acid is employed in surgery as dusting powder, as saturated (4%) aqueous solution, as boroglycerite, and in collyria (1 to 2% of boric acid or sodium borate). Boric acid is a mild acid, and increases the acidity of the urine; borax acts as a weak alkali. It lessens the urinary acidity, and is used for cleansing. The acid and alkali characters are very weak. The borate ion has no other *therapeutic uses.*

The frequent employment of these substances for the **preservation of food,** particularly meat, butter and milk (see page 382) makes **the question of their toxicity** very important, and a great deal of work has been done along this line. It may be premised that boric acid and borax behave exactly alike. A man living largely on preserved food may ingest as much as 0.5 Gm. of boric acid (or its equivalent in borax) per day; the consumption would generally fall below this figure. All investigators agree that this quantity has no immediate action of any kind in healthy individuals. When, however, the consumption is continued for a long time, quite marked effects are produced. The digestion becomes somewhat deranged; the body weight lessens; the feces become more watery (but there is no diarrhea even with larger doses). The absorption of fat and of nitrogen is somewhat diminished. The urinary nitrogen is slightly decreased, whilst the phosphates rise distinctly. The quantity of urine is scarcely altered. If a slight albuminuria was present, this is increased (Wiley, 1904). Boric acid therefore seems to have a *cumulative action* on digestion and absorption, metabolism, and the kidneys. The cumulative effect may be explained by the observation that the **excretion** of boric acid is slow, requiring several days. (However, it begins within ten minutes, and reaches its maximum in the second hour.) The excretion is not hastened by diuresis (Rost, 1905).

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* Not official.

The effects of such doses as are actually consumed would therefore not be very serious, even if the consumption of preserved food were continued for a long time. However, the results are somewhat deleterious, even in normal individuals; and they would probably be very undesirable in patients with digestive or renal disturbance.

Somewhat larger doses, 1 to 3 Gm. per day, produce the described effects more rapidly and more severely. Headaches appear. With 5 Gm., the subject soon becomes unable to do any work. Quantities above 2 Gm. per day may be condemned as distinctly harmful, without any hesitation. (Some investigators hold the opposite opinion.[1] Their results may probably be explained by individual differences of susceptibility, which were also noticed by Wiley.) Harrington, 1904, has observed that the continued administration of borax to cats leads to very severe kidney lesions. Very large doses cause **acute poisoning;** this may also occur from local administration. The symptoms consist ordinarily in gastroenteritis, congestion of the abdominal viscera, nephritis (granular degeneration), skin eruptions; very commonly visual disturbances, muscular debility and incoordination, fall of temperature, collapse. The autopsy shows fatty degeneration (Rinehart, 1901; Best, 1904).

MATERIA MEDICA.

Acidum Boricum (U. S. P.) [*Ac. Boracicum*, B. P.].— H_3BO_3. Soluble in 18 water, 15.3 alc., 4.6 glycerin (Sat. aqu. sol. = 5% = 25 grs. per ounce). *Dose:* 0.3 to 1 Gm. (5 to 15 grs.) (0.5 Gm. = 7½ grs. U. S. P.). As lotion, injection or gargle, 2 to 4%.

Unguentum Acidi Borici (U. S. P., B. P.).— 10% in white petroleum.

Liquor Antisepticus Compositus (U. S. P.).— See index.

Glyceritum Boroglycerini (U. S. P.) [*Glycerinum Acidi Boracici*. B. P.].— $C_3H_5BO_3$. 31% of boric acid. For external use, diluted 10 times.

Sodii Boras (U. S. P.) [*Borax*, B. P.] (*Sod. Biboras*).— $Na_2B_4O_7 + 10H_2O$. Sol. in 20.4 water, 1 glycerin, insol. in alc. *Dose:* as boric acid, also strength for external use.

Glycerinum Boracis (B. P.).—1 : 6.

Mel Boracis (B. P.).

XXI. URATES AND URIC ACID.

The importance of these lies in the fact that they may be formed or retained in excessive amounts in pathologic conditions, when they first produce inflammatory necrosis of cells, and are then deposited in insoluble granular form. This, becoming crystalline, acts as a powerful mechanical irritant, producing the phenomena of gout. These can be simulated in animals by the injection of suspensions of acid sodium urate, and in birds by the subcutaneous injection of chromates, or even by ligation of the ureters. The cause of the abnormal appearance of the uratic deposits in gout, etc., is not understood. It seems to be connected with changes in proteid metabolism, perhaps also with intestinal putrefaction.

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[1] For instance, Liebreich, 1903 and 1905.

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CHAPTER XXVI.

REMOTE (ION) ACTIONS OF ACIDS AND ALKALIES.

(A) ACTIONS COMMON TO BOTH.

1. Fourfold Action.— Acids and Alkalies exert a fourfold action:

1. By virtue of their *chemic* character, they produce, when fairly concentrated, profound changes in the body constituents, dead or living, and lead to destruction of tissue.
2. When dilute, they have an extensive and peculiar ion action upon the living protoplasm, due to the H and OH *ions*.
3. Like all other soluble and absorbable substances, they produce *osmotic* changes, and exert the ordinary salt action.
4. By influencing the action of ferments and the solubility of substances, they modify the processes of *digestion* and absorption.

The first, the purely chemic action, overshadows all others when strong solutions are applied. It will be studied in connection with corrosives in Chapter XXVIII.

The ion actions proper, the salt actions, and the effects upon digestion are most pronounced in dilute solutions, and these will be discussed in the present chapter.

2. Fate in Body.— Neither acids nor alkalies are absorbed unchanged from the alimentary canal. The alkalies (including the carbonates) are *neutralized* by the HCl of the gastric juice. Or if given in larger amounts, they enter into loose alkali-*proteid combinations* before they reach the blood. The acids undergo a similar change, or if they are not entirely absorbed before entering the intestine, they are there neutralized by the carbonates. The immediate effects, then, would consist only in altering the reaction of the alimentary canal, and in a certain amount of salt action.

However, there are other changes — more remote, but very important: The compounds with the proteids still possess the character of acids or alkalies; and even when the neutralization is effected by the HCl or Na_2CO_3, it is evident that the total amount of alkali in the body must be altered, at least temporarily. But since the organism is adjusted to work at a certain degree of alkaline reaction, which cannot be departed from without more or less severe modifications in its functions, it endeavors to counteract these changes in reaction. A *regulating mechanism* for this exists in the *formation of ammonia.*

This is normally produced as a precursor to urea; but the degree to which the final transformation takes place is easily modified by increasing or diminishing the fixed alkali of the blood. In the former case it is more complete; whereas if acid is introduced, the transformation does not take place, but the ammonia is excreted unaltered as a salt of this acid. It is therefore evident that acids and alkalies must influence the proportion of nitrogen which is excreted as ammonia and as urea. It is not inconceivable that this change introduces other modifications in the metabolism, but little is known about this.

If the ammonia formation is not sufficient to cope with the excess of acid or alkali, another mechanism for the maintenance of the normal reaction of the organism exists in the *rapid excretion* of any excess by the urine, in the form of acid or basic salts. (Free acids or alkalies never exist in the body beyond the alimentary canal.) Acids and alkalies are therefore very efficient *diuretics.*

On account of these mechanisms it is possible to give very large amounts of acids or alkalies to animals, by the mouth, without greatly altering the alkalinity of the blood.[1]

Their efficiency, especially against acid, is, however, not the same for all animals, and is conspicuously more perfect in carnivora, both as concerns the NH_4 and the elimination (Spiro, 1901) — probably because these are accustomed to ingest a certain amount of acid with their food. It is absolutely impossible to lower the alkalinity of the blood of a dog, to such a degree as to produce symptoms, by introducing acid into the alimentary canal, unless corrosion be produced. But if an acid or acid salt be injected into a vein, it will cause very pronounced symptoms, and these may also be produced in herbivorous animals if large quantities are given by the mouth. They will result in death even before the reaction of the blood has become neutral. So that it is not strictly correct to speak of an "acid action," but rather of the effects of diminished alkalinity (Kettner, 1902).

3. (a) These **acute effects of acid injection** — *i. e.*, of diminished

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[1] The alkalinity of the blood is most conveniently estimated by the CO_2 which it carries.

alkalinity of the blood[1]— fall upon the central nervous system, especially the medullary centers, and are mainly paralytic. The symptoms resemble asphyxia, and consist of coma, convulsions, depressed respiration and fall of blood pressure, etc. Death takes place by respiratory paralysis. These symptoms are at once removed — even in the last stages — by injection of Na_2CO_3 (F. Walter, 1877). This, as well as the fact that the serum in acid-poisoning is never saturated with CO_2 (Loewy and Münzer, 1901), shows that the cause of the fatality of diminished alkalinity is not due to the incapacity of the blood to take up the CO_2 formed in the tissues. The formation itself is diminished.

(b) **Diabetic Coma.**— These phenomena bear the closest resemblance to those of diabetic coma. Experimental investigation has, indeed, shown that the excretion of ammonia in this disease is always markedly increased, pointing to the presence of an abnormal amount of acid in the body.[2] This is oxybutyric acid; according to some, this again is formed from β-amidobutyric acid. As to the origin of the latter, little is known, but it could be derived from fats. The theory lay near to refer the phenomena of diabetic coma to acid-poisoning. Against this it was urged that the amount of this acid in the urine was insufficient to account for the symptoms. But plainly, it is not the excreted acid, but that retained in the body, which would be responsible for the effects; and it is claimed that recent calculations have shown that the alkalinity of the body is diminished to such a degree as to suffice for the explanation of the symptoms (Magnus-Levy, 1899).

The rational *treatment,* then, for this condition would be the administration of alkali in sufficient quantity, just as in the case of acid-poisoning in the rabbit. When this has been done in the proper manner the results have been fairly satisfactory. The principal difficulty has been that a sufficient amount of alkali was not used. If the alkali is administered by the mouth, in the early stages before coma sets in, it should be given in a dose of about 40 grams of sodium carbonate a day; and if coma has already set in, the quantity should be 100 or 200 grams. Carlsbad salt is also useful in this connection.

If such large quantities of sodium carbonate are taken, they will produce a cathartic effect. This purging may not be entirely useless, for it is conceivable that the underlying cause of the diabetes is found in toxins formed in the alimentary canal. At all events, plain purges have been found useful in such cases, and so has pilocarpin, used on the theory that it helps the elimination of the "toxins." But if catharsis occurs after sodium carbonate, so much may pass into the stools that it may be impossible to secure the absorption of a sufficient amount of alkali. In this case it should be given by intravenous injection of 0.3% solution of the crystallized salt. (Hypodermic injection is apt to cause sloughing.)

It will not do to wait with the administration of the alkali until the coma actually sets in, for it may then be too late. Diabetic coma differs in this respect from the acid-poisoning in the rabbit. The reason is, that in the latter the diminished alkalinity exists mainly in the blood, and may be readily influenced by the injected alkali; whereas in diabetic coma the acid is formed inside the cells, into which the alkali penetrates with more difficulty.

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[1] The *alkalinity of the blood,* as well as its CO_2, is also lowered by phosphorus, arsenic, and other metals, and in diabetes. It is increased in pregnancy, as also by salts of organic acids, which may be contained in the diet.

[2] It must not be supposed that an increase of ammonia in the urine always indicates an increased formation of acid. It may as well be due to changes preventing the ultimate steps in nitrogenous metabolism, *e. g.,* in hepatic diseases.

4. General Effect upon Metabolism.— The effects of *lesser changes in the reaction of body tissues* must be rather limited, since these are so promptly brought back to normal. Whilst it cannot be doubted that such changes must have an influence upon metabolism, the nature of this cannot be stated, because it is complicated by the actions of these substances on the alimentary canal. The latter is different in the case of acids and alkalies. Some of the other actions also require separate consideration. *Organic Acids* and their salts are rapidly burned to carbonate after their absorption; so that they act as acids only in the alimentary canal, but as alkalies after they are absorbed (Buchheim, 1888).

(B) EFFECTS OF DILUTE SOLUTIONS OF ACIDS.

1. On the Alimentary Canal.— (a) Mouth.— Acids have a characteristic *"sour" taste,* and are slightly astringent in the mouth. This taste determines their use as flavors.

The addition of acid also makes it possible to take much larger quantities of cold water than could be taken without. They are therefore of therapeutic value in *fevers,* when one wishes to obtain at the same time the refrigerant action of cold and the diuretic effect of large quantities of fluid. They soften the enamel of the *teeth,* and should therefore be taken by means of a glass tube. They also reflexly increase the flow of *saliva,* but this is of little practical importance.

(b) In the **stomach** their importance lies in the fact that *pepsin* cannot act except in the presence of acids. While any acid may answer for this purpose, hydrochloric seems to be the best, and is most efficient in the concentration existing in the gastric secretion; it also aids in the *solution of the connective tissue* of meats; and it determines the *antiseptic* qualities of gastric juice.[1]

The injection of dilute acid also increases the motor activity of the stomach, and the secretion of gastric juice. The latter effect is partly reflex, for it is observed in Pawlow's separated stomach (Bickel, 1905).

(c) Intestine.— Acids increase the flow of *pancreatic juice.*

This action is perhaps partly reflex, but it has been shown (Bayliss and Starling, 1902) that the presence of acid in the jejunum leads to the production of a chemic substance, "secretin," the intravenous injection of which stimulates the pancreas to increased secretion.

If free acid penetrates into the intestinal canal it acts as a very powerful irritant and produces increased *peristalsis.* Acids given by the mouth, however, are usually absorbed before passing the pylorus, so that this cathartic action is seen practically only when acids are generated in the intestine itself. There are, however, certain difficultly soluble acid salts, such as potassium bitartrate (cream of tartar), which are not dissolved in the stomach, and which may therefore extend their acid action to the intestinal canal. These acid salts are more strongly cathartic than ordinary salts under the same conditions.

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[1] Nascent HCl, generated by administering acetyl chlorid, is said to possess these qualities in a higher degree (Spinneau, 1901). The reaction which occurs is: $C_2H_3O.Cl + H_2O = HCl + C_2H_3O_2H$.

The presence of free acid in the duodenum causes closure of the pylorus, and thus opposes the expulsion of the gastric contents.

2. On Urine.— Acids are markedly diuretic; this is in part a salt action, in part due to the H ion. The urine will become more acid (due to acid salts, not to free acids).[1] This leads to an *increased irritability of the mucous membranes* of the urinary passages, so that inorganic acids are to be avoided in all inflammatory conditions of these organs. They must also be avoided where there is a tendency to the formation of uric acid *calculi.* On the other hand, they are indicated with phosphatic calculi. It may be repeated that they increase the ammonia of the urine at the expense of the urea.

3. Effects upon Metabolism.— Outside of this change in the ratio of ammonia and urea, these are quite small, as far as our present means allow us to judge. The excretion of nitrogen seems to be pretty constantly slightly increased.

Applied directly to *excised organs,*— muscle, nerve, etc.,— the result is an increase and subsequent diminution of function.

4. Therapeutic Uses of Dilute Acids.— Their importance as flavors and for the introduction of cold liquids — the latter preferably as lemonade — has received mention.

The *diuretic action* cannot be utilized, since they are too irritant.

They are extremely useful in cases of *dyspepsia* in which an insufficient amount of acid is secreted. Hydrochloric and nitro-hydrochloric acids are preferred for this purpose, and these act best when combined with bitters. They would be contraindicated in catarrhal conditions, in which there is a hypersecretion of mucus. Even in normal individuals the prolonged administration of large quantities of acids is apt to prove too irritant, and interferes with digestion. This is the explanation of the popular use of vinegar to reduce

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[1] Dunlop, 1896.

obesity. A direct limitation of diet would seem a more rational means for this purpose.

The increased flow of pancreatic juice, and perhaps also of bile, which has been ascribed to acids, is probably too small to be of any value.

The *increase of peristalsis* produced by acid salts is of considerable importance. It may be obtained by cream of tartar. This has the advantage over the ordinary cathartics in that smaller doses suffice, nor is its taste as disagreeable.

Their use in *fevers* depends partly upon the diuresis and diaphoresis due to the increased introduction of liquid. It is also claimed that the alkalinity of the tissues is raised in febrile conditions, and that this is counteracted by acids. Phosphoric acid in large doses (10 Gm. diluted with 300 c. c. water) is said to depress the heart and slow the pulse, but would have no advantage over aconite for this purpose.

5. Materia Medica of Acids.—

(A) Summary.

The small letters following the name of the acid refer to the more detailed description (pp. 588 to 592). The numbers refer to the brief description of the acids, given on page 588.[1]

Acids may be divided into inorganic and organic.

The inorganic acids, again, into *Hydracids,* containing the element in combination with hydrogen.
Oxyacids, containing oxygen.
Anhydrids, which yield true acids only after taking up H_2O.

TABLE XIII.—IMPORTANT INORGANIC ACIDS.

I. Inorganic. (These are all soluble in water or alcohol.)

		B. P.	U. S. P.	
		Per Ct. of Pure Acid by W'ght.	Per Ct. of Pure Acid by W'ght.	Specific Gravity
Hydracids.	*Acidum Hydrochloricum* (a), HCl (2, 4) (see below)	31.79	31.9	1.158
	Acidum Hydrochloricum Dilutum (3, 4)	10.58	10.0	1.049
	Acidum Hydrocyanicum Dilutum, HCN (1, 4)	2.00	2.0	....
	Acidum Hydrobromicum Dilutum (b), HBr (1, 3, 4)	10.00	10.0	1.076
	Acidum Hydriodicum Dilutum, HI (c) (1, 4)	....	10.0	1.106
	Syrupus Acidi Hydriodici.	....	1.0	....
	Acidum Hydrosulphuricum, H_2S (1, 4)	....	....	....

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[1] The strong mineral acids are incompatible with organic substances and with each other. All acids are incompatible with carbonates and bicarbonates, sulphids and sulphites, salicylates, benzoates, borates, etc.

		B. P.	U. S. P.	
		Per Ct. of Pure Acid by W'ght.	Per Ct. of Pure Acid by W'ght.	Specific Gravity
	Acidum Nitricum (d), HNO_3 (2, 4)	70.00	68.0	1.403
	Acidum Nitricum Dilutum (3, 4)	17.44	10.0	1.054
	Acidum Nitrohydrochloricum (e) (2)	....	....	....
	Acidum Nitrohydrochloricum Dilutum (3, 4)	....	....	....
Oxyacids.	*Acidum Phosphoricum* (f), H_3PO_4 (2, 4) (Concentratum, B. P.)	66.30	85.0	1.707
	Acidum Phosphoricum Dilutum (3, 4)	13.80	10.0	1.057
	Acidum Sulphuricum (g), H_2SO_4 (2, 4)	98.00	$>$92.5	$>$1.826
	Acidum Sulphuricum Dilutum (3, 4)	13.65	10.0	1.067
	Acidum Sulphuricum Aromaticum (3)	13.80	20.0	0.933
	Acidum Hypophosphorosum, HPH_2O_2 (1, 4)	....	30.0	1.130
	Acidum Hypophosphorosum Dilutum, HPH_2O_2 (1, 3, 4)	....	10.0	1.042
	Acidum Boricum, H_3BO_3 (1, 5)	....	....	....

Anhydrids.	*Arseni Trioxidum* = *Acidum Arsenosum*, As_2O_3 (1, 5)	....	....	....
	Chromii Trioxidum = *Acidum Chromicum* (h), CrO_3 (2) (Yellow solid)			
	Acidum Sulphurosum (i) SO_2 (1, 4)		$>$6.0	$>$1.028

II. Organic Acids.

Those of the Fatty Series are alone available for their acid character. (It will be recalled that this exists only locally, but disappears on their absorption. They are all soluble in water, with the exception of Oleic and Stearic Acids.)

(*A*) *Acids of the Fatty Series.*—The official acids belong to the following chemic groups:

1. *Monobasic Acids*, $CnH_{2n+1}CO_2H$.
    - *Acidum Aceticum* (k), $HC_2H_3O_2$ (U.S.P., 36%; Sp. G., 1.045) (2, 4) [B.P., 33%].
    - *Acidum Aceticum Dilutum* (U.S.P., 6%; Sp. G., 1.009) (3, 4) [B.P., 4.27%].
    - *Acidum Aceticum Glaciale*, >99% (2, 4) (U. S. P., B. P.); Sp. G., < 1.049.
    - *Acidum Trichloraceticum*, $HC_2Cl_3O_2$ (2, 5) (U.S.P.) (k.).
    - * *Acidum Formicum* (l), HCO_2H.
    - *Acidum Stearicum* (m), $HC_{18}H_{35}O_2$ (1, 2, 5) (U.S.P.).
2. *Dibasic Acids*, $CnH_{2n}(CO_2H)_2$.
    - *Acidum Oxalicum* (n), $H_2C_2O_4 + 2H_2O$ (1, 5).

* Not official.

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3. *Oxymonobasic Acids,* $CnH_2n(CO_2H)(OH)$.
   Acidum Lacticum (o), $HC_3H_5O_3$, 75% (2, 4) (U.S.P., B.P.).
4. *Dioxydibasic Acids,* $CnH_2n{-}_2(CO_2H)_2(OH)_2$.
   Acidum Tartaricum, $H_2C_4H_4O_6$ (5) (U.S.P., B.P.) (r).
5. *Oxytribasic Acids,* $CnH_2n{-}_3(CO_2H)_3OH$.
   Acidum Citricum (p), $H_3C_6H_5O_7 + H_2O$ (5) (U.S.P., B.P.).
6. *Monobasic Acrylic Acids,* $CnH_2n{-}_1(CO_2H)$.
   Acidum Oleicum (q), $HC_{18}H_{33}O_2$ (1, 2). Brownish Liquid (U.S.P., B.P.).

(*B*) *The Acids of the Aromatic Series* are never used for their acid character.

III. Acid Salts.

Potassii Bitartras.—Cream of Tartar.— $KHC_4H_4O_6$. Soluble in 200 parts of water. *Dose:* Diuretic, 1 to 3 Gm. (15 to 45 grains) (2 Gm. = 30 grs., U. S. P.); purgative, 4 to 15 Gm. (1/8 to 1/2 ounce).

Brief Description:

(1) Not used therapeutically as acids.
(2) Used only externally.
(3) *Dose:* 0.1 to 1 c.c. (1 to 15 minims). Diluted in half a tumbler of water, best taken through a glass tube.
(4) Colorless liquid.
(5) Colorless or white solid.
(6) All the U. S. P. dilute acids contain 10%, with the exception of Acetice (6%), and Hydrocyanic (2%).

(B) Details.

(a) *Acidum Hydrochloricum* (Muriatic Acid); *Prepared* by heating NaCl and H_2SO_4 and dissolving the gaseous HCl thus formed in water. The crude acid is obtained as a by-product in chemic industry. The strong acid gives fumes when brought near ammonia, or even in the air, due to the formation of NH_4Cl.

The *commercial acid* (strength = 30% to 33%) has a golden yellow color due to Fe and free Cl. Since it often contains As, it should not be used in internal medicine.

(b) *Acidum Hydrobromicum Dilutum:* Prepared by decomposing $BaBr_2$ with H_2SO_4. It has been used as a nervous sedative, but its usefulness as compared with potassium bromid is more than doubtful. The acid sometimes acquires a yellow color, due to the liberation of Br. It should not be employed in this condition.

(c) *Acidum Hydriodicum:* On account of its ready decomposition of the free air, this acid is generally in the form of *Syrupus Acidi Hydriodici.* This is made by decomposing KI with Tartaric Acid. The keeping qualities are improved by the addition of Potassium Hypophosphite. The syrup keeps better in direct sunlight. It is used for its iodin rather than for its acid qualities.

(d) *Acidum Nitricum:* Made by decomposing $NaNO_3$ by H_2SO_4 and distilling the product.

The official concentrated acid is colorless, emits fumes of hyponitrous acid when exposed to air, and acquires a yellow color. It stains organic matter yellow; this is changed to orange by alkalies.

Important are also:

**Acidum Nitricum Technicum:* Commercial Nitric Acid (Aqua fortis), 60% to 64%.

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* Not official.

Acidum Nitricum Fumans: Almost absolute HNO_3 saturated with NO_2.

The concentrated acid is used as a caustic (glass rod); against hyperhydrosis of feet (1 to 2 oz. to pail of water); as disinfectant (will corrode metal vessels or pipes).

(e) *Acidum Nitrohydrochloricum* (Nitromuriaticum) (U.S.P., B.P.) (Aqua Regia): Made by mixing 1 volume concentrated HNO_3 with 4.5 volumes HCl in an open vessel and allowing the mixture to effervesce. The composition is somewhat variable, but the final product contains NOCl and Cl_2 besides the two original acids. It is therefore a very powerful solvent and oxidizer.

The *dilute* acid is made by diluting the above with 3½ volumes of water. That of the British Pharmacopœia is somewhat more dilute. On account of the free chlorin, it may be supposed to have a stronger local irritant action than HCl. It is popularly supposed to "stimulate the liver," but its action does not differ in kind from that of other acids.

(f) *Acidum Phosphoricum:* Phosphoric Anhydrid (P_2O_5) forms three acids:

$$\begin{aligned} P_2O_5 + H_2O &= H_2P_2O_6 = 2(HPO_3) &&= \text{Metaphosphoric Acid.} \\ P_2O_5 + 2H_2O &= H_4P_2O_7 &&= \text{Pyrophosphoric Acid.} \\ P_2O_5 + 3H_2O &= H_6P_2O_8 = 2(H_3PO_4) &&= \text{Orthophosphoric Acid.} \end{aligned}$$

The last is the one official. It forms three series of salts; thus,

NaH_2PO_4, acid sodium phosphate.
Na_2HPO_4, neutral sodium phosphate.
Na_3PO_4, basic sodium phosphate.

It is prepared by burning phosphorus, dissolving the oxids in water, and completing the oxidation with HNO_3.

Phosphoric acid is said to be less detrimental to digestion than other acids; the evidence for this statement is rather weak.

(g) *Acidum Sulphuricum:*

Preparation.— The commercial ("English") Sulphuric Acid is made on a large scale by burning pyrites (impure iron sulphid) or native sulphur. The SO_2 is oxidized by means of nitrous fumes produced by the action of concentrated H_2SO_4 on Chili saltpeter ($NaNO_3$). The product is condensed in a system of leaden chambers in the presence of steam, and concentrated first in leaden pans and then distilled from glass or platinum retorts.

Characters.— The official acid is an oily, colorless liquid, acquiring a brown color if exposed to dust. Very intensely corrosive, charring organic substances. Miscible in all proportions with water or alcohol, with the evolution of much heat. (Such mixing must be done very cautiously by slowly pouring the *acid into the water,* under constant stirring.) It has a specific gravity of 1.835, and boils at 338° C., distilling without decomposition.

Uses and Dose.— As other inorganic acids. Very frequently used for the liberation of gases (SO_2, H_2S, etc.), for which purposes it is best diluted with 4 volumes of water. It is also used for filling the porous cup in Daniel batteries (diluted with 8 volumes of water).

The **Commercial Sulphuric Acid* (Oil of Vitriol) is very apt to contain arsenic, and should not be employed in medicine.

Aromatic Sulphuric Acid is a mixture of H_2SO_4 and alcohol, containing ethyl-sulphuric acid. It is doubtful whether it possesses any advantage over other acids.

(h) *Chromii Trioxidum* (U. S. P.).— *Acid Chromicum:* Chromic Acid, Chromic Anhydrid. CrO_3. Made by decomposing Potassium

---

* Not official.

Bichromate with Sulphuric Acid and crystallizing: $K_2Cr_2O_7 + H_2SO_4 = K_2SO_4 + H_2O + 2CrO_3$. Very soluble in water; decomposes all organic liquids, often with explosion. Melts at 192° C. Used only externally as an astringent irritant (1% to 15%), or concentrated as a caustic. Also used against sweating feet (5% solution).

(i) *Acidum Sulphurosum:* Sulphurous Acid. A solution containing at least 6.0% of Sulphur Dioxid (SO_2).

Preparation.— Sulphuric Acid is made to act upon charcoal, and the SO_2 is dissolved in water. (For small quantities, extemporaneously, it suffices to act on Na_2SO_3 with H_2SO_4.)

It must be kept in small glass-stoppered amber-colored bottles.

Character.— Colorless liquid of characteristic odor.

Uses.— As antiseptic in skin and parasitic disease, etc. Against gastric fermentation 1 c. c. (15 ♏), diluted.

SO_2, generated by the combustion of sulphur, is a favorite disinfectant for rooms.

* *Acidum Osmicum:* OsO_4. Used only in histology for fixing tissues.

(k) *Acidum Aceticum:* Acetic Acid. $C_2H_3O_2H$.

Acid. Acetic. Glaciale: Glacial Acetic Acid. Nearly or quite absolute Acetic Acid. Congeals at somewhat below 15° C.

Acidum Aceticum: Acetic Acid, of a strength of 36% by weight. This corresponds approximately to the No. 8 acid of commerce.

Acid. Acetic. Dil.: Dilute Acetic Acid. Made by mixing 100 Gm. of Acetic Acid with 500 Gm. of distilled water. It contains 6% by weight.

* *Acetum:* Vinegar. A dilute impure acetic acid, of a strength of 6%, obtained by the fermentation of vinous liquors. That made by the "rapid process" from dilute alcohol is the one preferred in medical practice, but those obtained from wine, cider, etc., are also employed for domestic use. Vinegar serves the same purposes as dilute acetic acid, but is inferior to it in keeping qualities.

* *Acetum Pyrolignosum:* Pyroligneous Acid, Wood-vinegar. A product of the destructive distillation of wood, containing 5% to 7% Acetic Acid, some Methyl-alcohol, Acetone, and Tar.

Used externally to combine the effects of acetic acid and tar.

Preparation of pure *Acetic Acid:* Distillation of Sod. Acetate with Sulphuric Acid.

Preparations.— Besides those mentioned above, dilute Acetic Acid is used as a solvent in the class of aceta.

The dilute Acetic Acid is also often flavored with aromatics (Acid. Acet. Aromat., Ph. G.).

Dose:

Internally, Ac. Acet. Dil.: 5 to 10 c. c. (ʒj to iiss).
Externally and for gargles, dilute 1 : 6 (=1%).
Against corns, 36%.
In proportion of 1% is frequent addition to hair washes.

Acidum Trichloraceticum: $C_2Cl_3O_2H$. Prepared through oxidation of chloral. Used in substance or strong solution as a caustic; especially against warts; it is less painful than nitric acid. Very soluble in water, alcohol, and ether.

(l) * *Acidum Formicum:* *Formic Acid*, HCO_2H.

Formic acid, as official in Germany and Switzerland, contains 25% of the absolute acid. It is prepared by the action of oxalic acid on glycerin.

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* Not official.

It is used only externally as a counterirritant in the form of

* Spiritus Formicarum:

Formic Acid, 25%	2
Alcohol	35
Water	13

(Formerly prepared by macerating ants in alcohol.)

(m) *Acidum Stearicum:* Stearic Acid, $C_{18}H_{36}O_2$ (U. S. P.).

Preparation.— The official acid is the ordinary more or less impure commercial form, obtained by the decomposition of fats, especially tallow, with acid, either directly or after previous saponification, and separating the more liquid portion (Oleic Acid) by expression.

The solid product contains, besides stearic, also palmitic and other similar fatty acids.

Characters.— A hard, white, odorless and tasteless solid, soluble in alcohol and more readily in ether, melting at a temperature not lower than 56° C.

Uses.— To give consistency to salves and cerates.

(n) **Acidum Oxalicum:* Oxalic Acid, $C_2H_2O_4 + 2H_2O$.

Preparation.—(*a*) By the action of HNO_3 on sugar or starch, or (*b*) by fusing sawdust with a mixture of KOH and NaOH. For medicinal use it is purified by recrystallization.

Characters.— Small, colorless and odorless, very acid crystals. Soluble in 10 parts water or 2.5 parts alcohol. It is bibasic.

Uses.— Acts as a caustic, but should not be used, on account of its toxic action after absorption. It is mainly of importance on account of its toxicology, having often been taken in mistake for $MgSO_4$, etc. The chemic antidotes are lime-preparations (chalk).

(o) *Acidum Lacticum:* Lactic Acid, $HC_3H_5O_3$. 75%.

Preparations.— Invert sugar is subjected to lactic fermentation in the presence of zinc oxid. The zinc lactate thus formed is decomposed by H_2S, and the filtered solution is evaporated to the required degree.

Characters.— Syrupy, intensely acid, colorless, and odorless liquid. Miscible with water, alcohol, or ether.

Uses.— Caustic, especially for dissolving diphtheritic membranes (1 : 5). There are no indications for its use internally.

(p) *Acidum Citricum:* Citric Acid, $H_3C_6H_5O_7 + H_2O$ (tribasic).

Citric Acid is widely distributed throughout the vegetable kingdom, occurring either free or combined with K, Ca, or Mg. It exists in largest quantity in acid fruits of all kinds, usually along with Malonic and Tartaric and other vegetable acids.

Lemon juice is allowed to ferment, during which process the gummy matter precipitates. The proteids are removed by boiling, and the filtered juice is treated with chalk. The calcium citrate is decomposed by H_2SO_4, and the citric acid separated by crystallization. Large crystals. Soluble in 0.54 water, 1.55 alcohol.

Lemon juice contains 6% to 8% of the acids.

A large lemon contains about 4 Gm.

A 5 : 1000 solution makes the ordinary lemonade.

Externally it has been used in 10% to 20% solution to dissolve diphtheritic membranes.

An important use is against scurvy.

Syrupus Acidi Citrici, 1%. *Dose:* 5 to 20 c. c. (ʒj to iv).

Tamarindus (U. S. P., B. P.), Tamarind.— The preserved pulp of the fruit of T. Indica, Leguminosæ; India, Africa, and West Indies. This owes its activity to organic acids, especially citric. It is used as a laxative, in *doses* of 4 to 30 Gm. (1 to 8 drachms).

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* Not official.

(q) *Acidum Oleicum:* Oleic Acid, $C_{18}H_{34}O_2$.

Preparation.— An impure acid made by separating the liquid portion of the commercial acid after cooling to 5° C. This commercial acid is obtained as a by-product in the manufacture of stearin candles.

Characters.— A yellowish oily liquid, of a lard-like odor and taste; specific gravity, 0.895; insoluble in water, soluble in alcohol, ether, and solvents of fats; becomes semi-solid at 4° C.

Uses.— Pharmaceutically in the preparation of the oleates (see page 60); also in plasters and soaps.

(r) *Acidum Tartaricum* (U. S. P., B. P.): $H_2C_4H_4O_6$. Crystals or white powder, usually prepared from argol. Soluble in 0.71 water, 1.67 alcohol. *Dose:* 0.3 to 1.3 Gm. (5 to 20 grs.) (0.5 Gm. = 7½ grs., U. S. P.).

(C) EFFECTS OF DILUTE ALKALIES.[1]

1. On the Alimentary Canal.— (a) Soluble Alkalies.— By virtue of their salt action and their chemic nature, alkalies will produce an *irritation* of the mucous membrane of the stomach. Their local action cannot extend beyond this organ, since they are neutralized. This irritation will be stronger or milder — and accordingly harmful or useful — according to the concentration of the alkali and the amount introduced. A mild degree of irritation leads to a more efficient *absorption,* as in the case of plain salt action. The process of absorption will, in addition, be favored by a solution of the *mucus* which forms a lining to the walls of the viscus — mucin being more soluble in alkalies. The activity of the *pepsin* of the gastric juice will be reduced by them.

There has been considerable discussion as to the effect of alkalies on the *secretion of gastric juice.* It was formerly claimed that this is stimulated; but all of the later experiments indicate that it is rather diminished (Bickel, 1905).

(**b**) **On the Intestine.**— On the other hand, they will reduce the acidity of the chyme, and thus increase the alkalinity of the intestine, even if they are themselves neutralized and absorbed before reaching the duodenum. In this way they may favor the emulsification of *fats,* and the action of the *pancreatic ferments* if there is not sufficient alkali in the intestine. The *insoluble alkalies* — calcium carbonate — would have less action in the stomach and more in the intestine. Alkalies do not affect the secretion of bile (Rutherford, 1879).

(c) It is evident that these effects would offer ***no advantage in normal conditions.*** Experiments show that whilst small doses of alkalies have no effect upon the utilization of food, large amounts lessen it. It is to be presumed that the normal amount of mucous coating in the stomach supplies a needed protection; the neutralization of the HCl would practically end gastric digestion; and the normal acidity of the chyme is not sufficient to interfere with intestinal digestion, and indeed supplies a useful stimulus to the secretion of pancreatic juice. The neutralization of the gastric juice also destroys its bactericidal action. (Indoxyl may be caused to appear in large quantities in the urine of a normal individual by a liberal administration of chalk.)

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[1] The subject to 1890 is covered in the work of Stadelmann.

(d) But the facts are very different in **pathologic conditions;** *i. e.*, when there is a hypersecretion of mucus — as in gastric catarrh — or a hyperacidity as the result of fermentation. The former may line the gastric wall with a coating alike impermeable to the digestive secretions and products, and this the alkali will remove; whilst too great a percentage of free acid will cause severe and harmful irritation and interference with the action of ferments.

2. Effects upon the Secretion of Urine.— The *secretion of urine is increased* by all alkalies. This is due partly to the salt action, which is especially large since the alkalies possess a conspicuous penetrating power. In addition, one must also assume an ion irritation.

Precisely the same effect can be secured by the administration of salts of the *organic acids,* especially citrates or acetates, and this without causing any gastric disturbance, which latter may interfere with the administration of alkalies. The acetates are preferred, since they are the least cathartic of these organic salts.

The diuresis also increases the absolute amount of *all salts* excreted, although their percentage is, of course, lessened. The alkalinity of the urine is increased by an excess of basic salts. The urine is, in consequence, *less irritating* to the mucous membranes with which it comes in contact, and, at the same time, it is mildly stimulant.

To secure this alkalinity 7 Gm. of sodium carbonate or 15 Gm. of sodium acetate or citrate are required per day.

3. Effects upon Metabolism.— On account of the importance of the alkaline reaction of the tissues for their functions, it might be expected that any modification of this alkalinity would profoundly modify the general metabolism.

It is known that *alkalies favor oxidation;* and it has been found that they lead to an increased oxygen consumption and CO_2 excretion (Lehmann, 1884). This effect is not, however, very large — probably because the alterations in the reaction of the body are never very great. Experiments made to determine the effect on *nitrogen metabolism* have given somewhat variable results, and these were certainly not greater than might be expected from the pure salt action, or from the interference with digestion which would result from large doses.

(Doses as large as 13 Gm. sodium carbonate, 20 Gm. of sodium bicarbonate, or 40 Gm. sodium citrate do not influence the total nitrogen excretion.)

The *proportion of the urea-nitrogen is increased at the expense of the ammonia.*

As to any increase or decrease of *uric acid,* this has not at the present time been sufficiently demonstrated. The effect upon carbon metabolism is equally small and uncertain.

The benefit of *citric acid in scurvy* is purely an empirical result, for which there is at present no explanation.

Increase of alkalinity is said to heighten the *bactericidal power* of the serum and tissues.

4. Effect on Mucus.— Mucin is more soluble in alkaline media, so that the alkalies dissolve any accumulations of mucus or render them more fluid. At the same time they increase mucus-secretion through an irritant and ion action.

5. The application of alkalies to **isolated organs,** muscles, nerves, etc., usually results at first in an increase and then in a diminution of function. The addition of alkalies to the infused saline solution appears to aid in sustaining the *blood pressure* after hemorrhage (see page 181).

6. Therapeutic Uses of Alkalies.— (a) Digestion.— In catarrhal conditions alkalies would be useful throughout the alimentary canal by *dissolving the mucus* which lessens the permeability of the walls of these organs, preventing at once the pouring out of digestive juices and the absorption of the digestive products. It forms a similar impermeable coating about the masses of food. Further, the mere presence of a large amount of indigestible material — and tenacious mucus must be regarded as such — is in itself irritating.

In addition to this solution of mucus, the alkalies may be useful in counteracting the irritant effects of *excessive acidity.* The amount of acid normally present in the alimentary canal must be considered as the best condition for it, and varies quite widely in different individuals. A slight temporary increase in this is of no importance, and is used up by the proteids of the food. But if the acidity, especially of the intestine, is kept permanently high, a chronic irritation is set up, and leads to *gastrointestinal catarrh.* Such a permanent increase of the acidity may be caused by acid articles of diet — *e. g.,* sour wines, etc.— or it may be the result of fermentative processes. A rather rapid formation of acids is partly responsible for the *summer diarrhea* of infants.

When the acid is introduced from without, the principal indication is, of course, to put a stop to its introduction; if it is formed in the intestine, to neutralize the already-formed acid and to remove the means of its formation, so as to prevent its recurrence.

If the hyperacidity is in the *stomach*, it may be neutralized by any of the soluble alkalies, sodium bicarbonate being the most useful. If it is in the intestine, the soluble alkalies will not be advisable, because they are neutralized or absorbed before reaching the place where their action is desired. In this case the insoluble alkaline earths or their carbonates or bismuth are given. If neutralization without catharsis is required, calcium salts in the form of lime-water, chalk, or calcium phosphate would be employed. If the cathartic action is also desirable, magnesium, as the oxid or carbonate, may be used. Catharsis may also be obtained by the addition of vegetable cathartics, such as rhubarb or senna. A part of the beneficial action of bicarbonate may also be due to the mild motor irritation.

(**b**) **Urine.**— The *diuretic action* of alkalies is one which is very frequently employed. As has been pointed out, this is best secured by acetates, to avoid the local action of free alkalies on the alimentary canal. The *increased alkalinity* of the urine is useful in *inflammatory conditions* of the urinary passages, in which the acid urine acts as an irritant. The increased alkalinity has also caused the use of alkalies in gravel, on the theory that they dissolve the uric-acid calculi.

This use is based on the fact that, in the test-tube, free alkalies and their carbonates dissolve uric acid quite readily.

The conditions are, however, quite different in the body. Alkalies are not excreted as such, nor as carbonates. They cannot, therefore, convert free uric acid into soluble alkaline urates, but at most into acid urates which are almost as insoluble as uric acid itself. It would be absolutely impossible to effect in this way the solution of even very small calculi. At the same time, since the urine is less acid, the precipitation of phosphates will be favored, and this may increase the size of the stone. Lithium urate is especially soluble (Lipowitz, 1841), and the lithium carbonate was used against calculi as early as 1844 (Ure). But, as previously remarked, this solubility does not apply to the urine.

In some cases, however, alkali may be useful in reducing the acidity of the urine, and thus preventing further increase in the size of the stone. In several instances it has been observed that it caused the breaking up of large stones into small fragments. This cannot be attributed to a solution of the uric acid. The explanation is that probably the calculi were composed originally of small fragments glued together by mucus, and that the alkalies caused the solution of the latter.

Alkalies will also be useful in these conditions by lessening the irritability of the urinary passages. If alkalies are given at all for this purpose they should be in the form of acetates or citrates of potassium, since this metal forms more soluble urates than does sodium.

Certain **organic bases,** which are excreted in large part unchanged by the urine, are superior to the inorganic alkalies as urate solvents, forming compounds (even when uric acid is present in excess) which are much more soluble than lithium urate. This does not occur, however, if sodium salts are present,[1] so that there can be no solution of uric acid in the body or urine. Nevertheless, these bases have been extensively used for the treatment of lithiasis, gout, chronic rheumatism, arthritis deformans, etc. The results are no greater than could be expected from the diuretic action of these compounds. The only rational use is in the *irrigation of the bladder* for vesical calculi, when the sodium salts would not be present. A 1 to 5% solution of piperazin may be used for this purpose.

The most used of these organic bases is diethylen-diamin, better known as **Piperazin** [$(C_2H_4)_2 = N - N = H_2$]. Although it is quite alkaline, it is not irritant, nor toxic. Its quinate has also been employed, under the name of *sidonal*, since it was believed that quinic acid prevents the formation of uric acid, or converts it into hippuric acid. This statement is now denied (see Index). The quinate of lithium, "*urosin,*" has also been used. The tartrate of dimethyl-piperazin, "*lycetol,*" has some advantage over piperazin, in that it is non-hygroscopic, and more diuretic. The hydrochlorate of ethylen-ethenyl-diamin, "*Lysidin,*" is more solvent than piperazin. The base *Ethylen-diamin*, $C_2H_4 = (NH_4)_2$, dissolves coagulated proteids, and has been used for dissolving false membranes. The solvent action of *urotropin* has been discussed previously.

There appears to be still less reason to accept any solvent action of alkalies on uric-acid deposits in the tissues, although the alkalies, and especially lithium, are still extensively used on this theory in the treatment of gout. Others have attempted to explain their effects by assuming that they cause an increased oxidation of urates into urea. This also cannot be considered as demonstrated. Their employment would, therefore, be entirely empirical. The main reliance in the treatment of gout must still be placed upon proper diet and hygiene. Clinically, however, the alkalies are generally considered useful, especially in *chronic rheumatism*.

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[1] Vindevogel, 1901.

Their employment in *diabetic coma* has already been discussed. They are also employed against *obesity*, their effects being probably explained, like those of acid, by the derangement of digestion.

(c) **Mucus.**— The solution of mucus by alkali is of use not only in the intestinal canal, but in other situations. It is used in this way as an expectorant. It has also been used in catarrhal dysentery (enemata of 1 : 500 sodium bicarbonate). The false membranes of diphtheria, croup, etc., are also composed largely of mucus, and may be broken down by alkalies. They are best employed in this case in the form of a steam saturated with lime-water, commonly prepared by inhaling the vapors produced by slaking lime in the sick-room.

I. MATERIA MEDICA OF ALKALIES.

Alkalies are *incompatible* with acids, metals, and alkaloids.

HYDROXIDS AND OXIDS.

	One Part is Soluble in		Av. Dose (U.S.P.) (*Well diluted*)
	Water.	Alcohol.	
Sodii Hydroxidum (U. S. P.), NaOH. White pencils or crusts; used as caustic. 2% sol. on skin	1.	very sol.	....
Potassii Hydroxidum (U. S. P.) *Potassa Caustica* (B. P.) — KOH; as the preceding	0.4	2.	....
* *Potassa cum Calce* (Vienna Paste); caustic	....	....	....
Calx (U. S. P., B. P). CaO. Quick-lime. Caustic (paste)	760	insol.	....
Calx Hydrata (B. P.). $Ca(OH)_2$. Caustic	....	....	....
Magnesii Oxidum (U. S. P.) *Magnesia* (B. P.) — See Index	....	....	....

SOLUTIONS OF HYDROXIDS.

Liquor Sodii Hydroxidi (U. S. P.); 5%; caustic			1 c. c. = 15 ♏.
Liquor Sodii Ethylatis (B. P.); 18% of C_2H_5ONa in absolute alcohol; caustic...	....	....	....
Liquor Potassii Hydroxidi (U. S. P.) *Liquor Potassæ* (B. P.) — 5%; caustic..			1 c. c. = 15 ♏.
Liquor Calcis (U. S. P., B. P.). Saturated (0.14%)			16 c. c. = 4 ʒ.

	One Part is Soluble in		Av. Dose (U.S.P.) (*Well diluted*)
	Water.	Alcohol.	
Aqua Ammoniæ Fortior (U. S. P.), 28%, NH_4OH. Sp. G., 0.897. Caustic	....	....	....
Aqua Ammoniæ (U. S. P., B. P.), 10%. Sp. G., 0.958. Caustic			1 c.c. = 15 ♏.
Spiritus Ammoniæ (U. S. P.), 10%. Caustic			1 c.c. = 15 ♏.
Spiritus Ammoniæ Aromaticus (U. S. P., B. P.), ammonia and ammon.-carbon			2 c.c. = 30 ♏.
Linimentum Ammoniæ (U. S. P., B. P.), 35% ammonia water in cottonseed oil	....	....	....

CARBONATES.

	Water.	Alcohol.	Av. Dose
Potassii Carbonas (U. S. P., B. P.). K_2CO_3. For baths, 100 Gm.; for skin, 1.5%	0.91	insol.	1 Gm. = 15 grs.
Sodii Carbonas Monohydratus (U. S. P.). $Na_2CO_3 + H_2O$	2.9	insol.	0.25 Gm. = 4 grs. for bath, 100 Gm. for skin, 1.5%
Sodii Carbonas (B. P.). $Na_2CO_3 + 10H_2O$.			
Sodii Carbonas Exsiccatus (B. P.). Na_2CO_3			
Lithii Carbonas (U. S. P., B. P.). Li_2CO_3.	75.	insol.	0.5 Gm. = 7½ grs.
Ammonii Carbonas (U. S. P., B. P.). See Index	....	....	....
Magnesii Carbonas (U. S. P., B. P.). See Index	....	....	....
Calcii Carbonas. See Index	....	....	....

BICARBONATES.

	Water.	Alcohol.	Av. Dose
Potassii Bicarbonas (U. S. P., B. P.). $KHCO_3$	3.	alm. insol.	2 Gm. = 30 grs.
Sodii Bicarbonas (U. S. P., B. P.). $NaHCO_3$ (0.6 to 4.0 Gm. = 10 to 60 grs.)	12.	insol.	1 Gm. = 15 grs.
Trochisci Sodii Bicarbonatis (U. S. P., B. P.)			each 0.18 Gm. = 3 grs.

SOAPS.

Sapo (U. S. P.)
Sapo Durus (B. P.)
{ *White Castile or Venice Soap*. Prepared from NaOH and olive oil. Enters into *Emplastrum* and *Linimentum Saponis*.

Sapo Animalis (B. P.).— From NaOH and animal fat.

Sapo Mollis (U. S. P., B. P.).— *Soft Soap*.— Made from KOH and linseed oil.

Soaps are soluble in hot water and alcohol.

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OTHER ALKALIES.

See Index for borates, acetates, citrates, and tartrates.

SO-CALLED URATE SOLVENTS.

* *Piperazin.*— White lustrous, almost tasteless, crystals, deliquescent, readily soluble in water or alcohol. Administered in dilute solution, 1 Gm. (15 grains) per day.

* *Sidonal.*— White tasteless powder, readily soluble in water or alcohol. *Dose:* 1 to 2 Gm. (15 to 30 grains), in dilute solutions.

* *Urosin* (Lithium quinate).—*Dose:* 0.5 Gm. (8 grains).

* Lycetol.— White powder, of slightly acidulous taste; non-hygroscopic. *Dose:* 1 to 2 Gm. (15 to 30 grains), in water.

* *Lysidin.*— Very hygroscopic, marketed as 50% aqueous solution. *Dose:* 1 to 5 Gm. (15 to 75 grains) per day, largely diluted.

(D) CARBONIC ACID IN SOLUTION (CARBONATED DRINKS).

These have primarily an acid action, but occupy a somewhat peculiar position. In the first place, CO_2 penetrates very readily on account of its volatility. Unlike other acids, the activity of carbonic acid is not destroyed by neutralization. When absorbed it is fixed in the form of sodium bicarbonate, which is dissociated so readily that it acts both as acid and alkali. For this reason the action of carbonic acid is at once extensive and mild. Taken by the mouth it increases the absorption of food and especially of liquids. In this way it is of very great benefit in fevers. It has also a somewhat specific effect in diminishing vomiting. On account of the stimulation of the sensory nerves of the mucous membranes with which it comes into contact, it is a general reflex stimulant (Quincke (1877).

(E) MINERAL WATERS.

These will be discussed more in detail in other places, according to their ingredients, but the whole subject may be very briefly summarized in the following compilation:

The action of natural mineral waters has been known empirically since remote times. Their use came about probably by accidental observation and also through the marked taste which they possess.

Spring and Artificial Mineral Waters.— A very striking observation was early made, namely, that these mineral waters, when used at their source, appear to be more effectual than artificial compounds of practically the same composition, or even than the same water when used at a distance.

The most diverse explanations for this have been advanced. Especially in the case of thermal waters, so-called tellurial forces, some mysterious property imparted to them by the earth, have been invoked. Since the discovery of radium, it has been found that some mineral waters are slightly radioactive, and this has been used to explain their action: but this is not at all demonstrated, and is doubted by most authorities. Others, again, have laid great stress upon the presence of minimal traces of rare elements, somewhat upon the homeopathic principle. Still others believe that the artificial waters — even if they contain the same elements in the same proportion — do not contain them in the same state of combination; for instance, that the artificial water would contain NaCl and $MgSO_4$, the natural water $MgCl_2$ and Na_2SO_4. This is, of course, contrary to the demonstrated facts; all solutions containing the same proportions of the same ions, will have these ions present in the same state of combination, no matter what particular salts were used to introduce these ions. There is nothing in any of these theories. Mineral waters are simply solutions of the ingredients of the soil, and possess only the action of those ingredients which are present in notable amount.

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* Not official.

The difference between the water of natural sources and the artificial solutions rests upon other causes, which are sufficiently easy to appreciate, but difficult to reproduce.

These factors refer largely to hygiene and climate. A large proportion of the effects must be attributed to the rest, the freedom from care and business pursuits, the exhilarating effect of improved hygienic, atmospheric, and scenic conditions, better regulation of all the habits, of diet, exercise, etc. The mere drinking of large quantities of fluid is also something which it is difficult to enforce at home, but which the patient does regularly in watering-places. Added to these comes finally the specific action of the dissolved salts.

The effect of mineral *baths* is purely local and reflex. There is *no absorption* of the dissolved salts through the skin. The effects are in general the same as with hydrotherapeuty, excepting that they are somewhat stronger.

The waters of mineral springs vary in **temperature;** those below 28° C. are called cold; 25 to 37.5°, warm; above this, hot. The higher temperatures favor absorption, and are therefore more favorable for alkaline waters; cold causes motor stimulation of the alimentary tract, and is preferred for cathartics.

The **molecular concentration** of mineral waters varies considerably; the depression of freezing point is 1.0150 for Hunyadi and Apenta; 0.320 for Vichy; 0.275 for Carlsbad; 0.240 for Apollinaris; etc. (Kostkewicz, 1899).

Classification.— These waters are usually classified according to the contained salts. Various classifications are current. The following will be used here:

1. Plain Saline (NaCl).
2. Carbonated:
   - (*a*) Plain.
   - (*b*) Alkaline ($NaHCO_3$).
   - (*c*) Saline (Na_2SO_4).
3. Magnesia.
4. Sulphur.
5. Chalybeate.

Occasional constituents of small importance are Ca, I, Br, Li, and As.

The physiologic effects of the majority of these constituents will be discussed under their respective headings, and will only be very briefly alluded to in this place. It will also be impossible to take up the composition and special indications of the different mineral waters, in anything like an exhaustive manner. It will be necessary to illustrate these classes on only a few well-known waters. It need scarcely be mentioned that the above classification is not an absolutely sharp one, but that many mineral waters belong partly to several classes.

1. Plain Saline Waters.— These are used mainly externally for baths. The most typical is sea-water.

The composition of this is somewhat different in different oceans. In the English channel it is as follows:

1,000 parts by weight contain:

NaCl	27.0
KCl	0.75
$MgCl_2$	3.7
MgBr	0.027
$MgSO_4$	2.3
$CaSO_4$	1.4
$CaCO_3$	0.03
Iodids, etc.	traces.

The freezing point of sea water is: —2.29° C. at Naples (Bottazzi, 1897); —1.90° at Pacific Grove, California; and —1.82° at Wood's Hole, Massachusetts (Garrey, 1905).

Artificial sea-baths may be made by dissolving 4% of sea or rock salt in water.

Some of the important saline sources are the following:

European:

	Per 1,000: Fixed Salts.	NaCl.	Temperature (C.).
Kissingen[1]	15	11	18.5°
Baden-Baden	28	21	18.5°
Nauheim	30	25	33.0°

American: Saratoga Congress, New York, approaches Kissingen.

2. Carbonated Waters.— (a) Plain.— In these the CO_2 is the main constituent. This aids digestion, and these waters are used mainly as plain table waters. The most used is the artificial soda-water.

An example of a natural carbonated water is Apollinaris:

Per 1,000 Gm.:

$NaHCO_3$.	NaCl.	Na_2SO_4.	CO_2.	Temp.
1.2	0.4	0.3	1.5	21°

(b) Alkaline.— These contain a notable amount of $NaHCO_3$. They have the alkaline effects and are therefore useful in gastric catarrh, hyperacidity, hypersecretion of mucus, and as diuretics, in obesity, gout, urate stones, and diabetes. They are most useful when taken hot and drunk very slowly, since in this way they cause the least irritation in the stomach.

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[1] *Formula for Artificial Kissingen* (N. F.):

Potassium Chlorid	17
Sodium Chlorid	337
Magnesium Sulphate	59
Sodium Bicarbonate	107

Twenty-four grains of this to 6 ounces of water (half a teaspoonful to a tumbler) is the usual dose.

(c) **Alkaline Saline Waters.**— These waters usually contain in addition some Na_2SO_4. The indications for use are the same as for the preceding. The cold waters contain more CO_2 (Marienbad and Franzenbad). The hot alkaline waters are very numerous. The following may be taken as examples:

European Carbonated Alkaline Waters, per 1,000:

	$NaHCO_3$.	Free CO_2.	NaCl.	Na_2SO_4.	TEMP.
Vichy[1]	5.0	500	..	0.2	40°
Ems	2.0	500	1.0	..	40°
Selters	1.2	1,200	2.3	..	cold.

Spa, Pyrmont, Wiesbaden.

American: Saratoga Selters, Saratoga Vichy, Sweet Springs of Virginia, Gettysburg, etc.

(**d**) Of the *Carbonated saline waters* the most representative is the *Carlsbad*. The formula for the artificial salt is:

K_2SO_4	0.12
Na_2SO_4	2.64
$NaHCO_3$	2.16
NaCl	1.08
	6.00 Gm.

This quantity (a teaspoonful) is the proper amount for a liter (quart) of water.

3. **Magnesia Waters.**— These contain $MgSO_4$, Na_2SO_4, $CaSO_4$, $MgCl_2$, but no CO_2. They are useful as cathartics. If they contain $CaCO_3$, the alkaline action extends deeper into the intestine than in the case of $NaHCO_3$.

European, in 1,000 Gm.:

	$MgSO_4$.	Na_2SO_4.	$CaSO_4$.	NaCl.	$MgCl_2$.
Hunyadi János ..	22.3	22.5	..	1.3	..
Seidlitz	13.5	...	1.4	..	0.4

Epsom and Friedrichshall belong to the same class.

American: Crab Orchard, Kentucky, and Bedford Springs, Pennsylvania.

4. **Sulphur Waters.**— These contain free H_2S and sulphids. Externally they stimulate the skin and soften the

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[1] *Formula for Artificial Vichy* (N. F.):

Sodium Bicarbonate	846.0 Gm.
Potassium Carbonate	38.5 "
Magnesium Sulphate	38.5 "
Sodium Chlorid	77.0 "

Fourteen grains to 6 ounces of water (¼ teaspoonful to a tumbler) is the dose.

epidermis; internally they act as cathartics. They have considerable reputation in the treatment of chronic rheumatism. Some examples are: Aix-la-Chapelle, Harrogate, Virginia Sulphur Springs. The following will give an idea of their composition:

In 1,000 Gm.:

	Free H_2S.	Na_2SO_4.	NaCl.	TEMP.
Aix-les-Bains	0.003	0.092	0.030	44°

5. Chalybeate Waters.— These contain Fe, usually as bicarbonate, also NaCl and Na_2SO_4. The amount of iron is from 0.01 to 0.12 of FeO per liter. The most famous springs are: Tunbridge and Brighton in England; Pyrmont, Wiesbaden, and Spa on the Continent; Bedford, Pittsburg, Brandywine, and several Virginia springs, in the United States.

(F) CLIMATE.

This is of such great importance in the action of mineral waters that it may be discussed in this place. Only the roughest sketch can be given, and the student must refer to larger text-books for further description.

The principal elements which enter into the climate are the following:

1. Air:
    - Purity.[1]
    - Density (Altitude).
    - Moisture.
    - Temperature.
    - Special Constituents.[2]
2. Sunlight.
3. Water, Purity of.
4. Conditions of Life — comfort, hygiene, rest, diversion, pleasant surroundings, out-of-door life, etc.

The subject of climatology is very largely empirical. The work which has been done on the effect of the different climates upon metabolism, nutrition, etc., is as yet too limited to be of great value.

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[1] Purity: This refers especially to the absence of bacteria, but other fixed impurities may also be of importance; *e. g.*, the causation of hay-fever by pollen. In cities, various chemic gases may also be deleterious impurities.

[2] Of such special constituents, the aromatic oils given off by needle-trees may be of considerable value as antiseptics in phthisis. The presence of ozone, if it is of any importance, serves mainly to indicate the general purity of the atmosphere.

The *principal climates used in therapeutics* are:

1. Sea.
2. Dry and Warm.
3. Elevated.

1. Sea Climate (Including Islands and Sea Voyage).— The important effects of this are related to constant temperature, humidity, and purity of the atmosphere, and to general surrounding conditions.

This climate, being very restful, is especially useful in cases of overwork. The freedom from atmospheric impurities also renders it valuable in hay-fever and phthisis.

2. Dry and warm climate, such as in deserts and Egypt, southwestern Texas, inland Southern California, or in the pine sections of Georgia and the Carolinas.

The special advantage of this climate consists in its permitting outdoor life in winter. It is peculiarly valuable in lung disorders which do not stand a northern temperature.

3. Elevated Climates.— These are generally aseptic, and the air is cool and dry. What importance can be given to the rarefaction of the atmosphere is not at present clear, still less the manner in which this acts.

The rate of the heart and respiration is at first increased, but later it returns to normal.

The quantity of urine is increased, as also the gaseous metabolism and respiratory quotient. The nitrogen excretion is diminished (Jacquet and Stähelin, 1901). The blood becomes rapidly more concentrated in corpuscles, and the serum in proteids. The absolute amount of corpuscles and of hemoglobin is not, however, much increased at first, but notably so later (Jacquet, 1904).

These climates cause improvement in a number of conditions, probably in part due to a greater exercise of the organs from climbing, etc. They are *useful* in dyspepsia, anemia, chlorosis, insomnia, asthma, and consumption.

High climates are *unfavorable* to feeble conditions of the heart and vessels, which cases should be sent to the seashore.

CHAPTER XXVII.

SYSTEMIC (ION) ACTION OF METALLIC SALTS.[1]

I. ABSORPTION, ETC.

Absorbable and Non-absorbable Metals.— In the case of metals one must distinguish between the local and remote actions. Every metallic salt has a local action; in addition, every metallic salt which is dissociable into ions has a toxic action if it is introduced into the circulation. It does not matter whether the metal is arsenic or iron; even the degree of the toxicity is practically the same in both cases if they are actually introduced into the body. (The alimentary canal is not, in this sense, "within the body.") The main difference between the two metals consists in the fact that arsenic is easily absorbed, while iron, like most other metals, is not.[2] Arsenic, mercury, and uranium are the only metals the absorption of which is of an extent sufficient to cause acute poisoning with non-corrosive doses. Phosphorus, which behaves pharmacologically in many respects like metals, is absorbed still more readily. Certain other metals are absorbed much more slowly. To this class belong lead, silver, tin, and iron. Any metallic salt, if given in strong solution, will cause *corrosion* of the mucous membrane of the alimentary canal and will then be absorbed, and would exert its systemic action were it not that the local effects often kill before the systemic can come into play.

A peculiarity of the corrosion produced in this manner is that there seems to be a possibility of acquiring a certain immunity to it. If the administration of a metallic salt is begun with small doses and gradually increased, it becomes possible to administer without effect doses which would at first have produced violent corrosion.[3]

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[1] The materia medica of all metallic salts (including those used only locally) will be given in this chapter. The nature and therapeutic uses of the local actions are discussed in Chapter XXVIII.

[2] Metallic poisons are generally more toxic to herbivora than to carnivora — probably because they remain longer in the alimentary canal of herbivorous animals, allowing greater absorption.

[3] Molds accommodate readily to metallic poisons.

To be absorbed, the metal must of course be in soluble form; but it must be borne in mind that the solubility in the alimentary canal is not necessarily the same as the solubility in water in a test-tube. In fact, it makes little difference, except as regards local action, in what form a metal is administered. In the stomach it will be converted largely into the chlorid; in the intestines into the carbonate and sulphid. Further, the metallic salts enter into double combinations with proteids, and these are often soluble in an excess of the latter. In this way such insoluble compounds as mercuric oxid, mercurous chlorid, lead sulphate, and silver chlorid, may be brought into solution.

Absorption is one factor necessary to produce the toxic action. A second factor is that the compound must contain the metal in a *dissociable form* — *i. e.*, in the form of ions. This is not the case with the pure metals nor with some organic compounds, such as

$$\mathrm{Zn}<\begin{matrix}C_2H_5\\C_2H_5\end{matrix};$$

nor with the iron of ferro- and ferricyanids. In these combinations the metals form a firmer part of the molecules. However, both the pure metals and the organic compounds are in most cases split up in the body into dissociable compounds, and so finally come to exert the metal action, but only after dissociation.

Colloid Metals occupy a peculiar position. Colloid metals may be obtained by establishing an electric arc between metallic wires under water, very fine particles of the metal being thrown off and forming a colloidal solution. Similar solutions may be obtained from solutions of metallic salts by certain reducing agents. Colloid solutions of Pt, Ag, Hg, Au, Bi, Cd, Pd and Ir have been prepared by these methods. The metal exists in these solutions, not as ions, but in true metallic condition; it is, however, so finely subdivided that it remains permanently and evenly distributed through the solution. It is precipitable by salts, in the same way as other colloidal solutions. These solutions cannot produce the ion-actions of the metals directly. The colloid condition, however, gives them *catalytic properties*, *i. e.*, minute quantities may induce reactions in large quantities of other substances (*e. g.*, conversion of alcohol into acetic acid), the metal taking no part in this transformation. This catalysis is hindered by many poisons, just as is the action of true ferments. The metals *pass quite readily from the colloid into the ionic condition*, *e. g.*, by the action of bacteria, and may then exert the ordinary action of the metals. Since this conversion occurs but slowly, these actions will be mainly local, and will produce a minimum of irritation. Colloid solutions of silver and mercury have therefore been utilized to moderate the effects of these metals. When injected into the body, the colloid metals produce a gradual cachexia. It is not possible to decide at present whether they do this through their catalytic properties, or by being converted into the ionic condition.

II. REMOTE ACTION.

The systemic actions of most metals can only be studied by injecting them intravenously, since the slow absorption and the strong local actions would obscure the remote effects, if the metals were given by the ordinary channels. For the intravenous injection, such metallic salts must be chosen as will not precipitate the blood. Double salts (such as iron-ammonium citrate, etc.) or metallic albuminates may meet this requirement. In some cases it is necessary to have recourse to some non-ionic compounds of the metal, from which the ionic metal is liberated in the body.

When such a preparation is injected directly into the blood the symptoms in many cases do not arise at once, but are *developed quite slowly,* sometimes only in the course of several days. This is due to the fact that the metals do not act in the blood, but only after they have been absorbed into the cells; and this absorption is so slow that it may take several days to accumulate sufficient metal to produce any action. It may by this time have disappeared entirely from the circulating liquids (White, 1880).

It would appear also that the symptoms do not arise immediately after the poison has reached the cells. Tartar emetic, when injected in appropriate doses into a vein, disappears from the blood in ten minutes, but the first symptoms can be seen only after some twelve hours. This corresponds with the behavior of toxins and of many other poisons.

The *excretion* of the metals is usually even slower than their absorption. They have therefore often a cumulative action; doses too small to produce any immediate effect will cause serious poisoning if long continued. Pb, Hg, and As are the most prominent examples of this. A single large dose may, on the other hand, produce chronic poisoning. In whatever manner the metal is introduced into the circulation — whether intravenously, hypodermically, or from the intestinal canal — it is excreted partly by the kidneys, but the main part leaves through the intestines, especially the large. The epithelial cells are the channel of this execretion, and not to any extent the bile, as was at one time supposed. A *gastro-enteritis* may result from local action even when the poison has been given intravenously. On this account tartar emetic, for instance, acts largely locally even when administered intravenously or hypodermically.

A sufficient amount of the metals, however, is excreted by the kidneys to cause a marked nephritis, characterized in the ordinary manner by albuminuria, casts, etc. The *nephritis* begins in the epithelium of the convoluted tubules and spreads from here to the glomeruli. If the poisoning is chronic, the nephritis may become interstitial and lead to renal cirrhosis. Nephritis has been described in poisoning by the following metals: Ag, Al, As, Au, Be, Bi, Cd, Ce, Co, Cr, Cu, Hg, Mn, Ni, P, Pb, Pt, Sb, U, W, Zn.

In their *systemic effects*, all the metals show a striking similarity. They affect mainly the circulation. There is a very marked *fall of blood pressure*, which is due partly to a *paralysis of the blood-vessels* and partly to a *direct action on the heart*. Secondary to this disturbed circulation there arise symptoms from the *central nervous system*. A direct effect upon nervous organs is not common in mammals, and is only conspicuous with silver.

Frogs show with most metals a paralysis, preceded by a slight stimulation. The tetanizing action predominates with Ni, Co, and Pt. Whether the metals have any direct effect on ***metabolism*** cannot be decided with our present methods, because of the disturbances introduced by the intestinal and renal irritation, and by the circulatory changes.

The metals, aside from silver, may be divided into ***two principal groups:*** the first group acting mainly peripherally on the ***blood-vessels***, the second group acting peripherally on the ***heart***. To the first group belong arsenic, antimony, uranium, bismuth, iron, manganese, selenium, tellurium, aluminum, tin, nickel, cobalt, gold, and platinum; to the second group, lead, phosphorus, copper, zinc, cadmium, mercury, vanadium, cerium, and thallium.

III. ARSENIC.

I. SUMMARY OF ACTIONS.

A *relaxation of the walls of the capillaries*, particularly of the splanchnic area, accompanied by an increased permeability, and consequently by changes similar to those of inflammation. As this is shown mainly in the splanchnic area, the most conspicuous symptoms are those of a *gastro-enteritis*, which resemble closely those of cholera.

This dilatation of capillaries introduces changes in the circulation which cause secondary disturbances in the function of more remote organs, particularly in the *nervous system;* and further, fatty degeneration of the cells, particularly in glands and muscles, with other disturbances in metabolism. There may also be a direct paralysis of the *heart*, both ganglionic and muscular.

Arsenic preparations possess a rather weak corrosive action.

II. DETAILS OF ACTION.

The action of arsenic may be either acute or chronic. Very little essential difference has been made out between the two, beyond some direct corrosion in the former. Both rest upon the paralysis of the capillaries.

1. **Acute arsenic-poisoning**[1] sets in very rapidly, pointing to a quick absorption. The first *symptoms* are of acute *gastro-enteritis,* and resemble so closely those which result from corrosive poisoning that they were formerly believed to be due to this. However, the autopsy rarely shows extensive corrosion, and it is known that the corrosive action occurs extremely slowly.[2] Furthermore, the gastro-enteritis may be obtained with at least equal readiness if the arsenic is injected into the circulation or subcutaneously. This would not definitely exclude all local action, since some arsenic is excreted into the alimentary canal; but the quantity is not nearly enough to account for the symptoms.

Simultaneously with the violent vomiting and purging of the gastro-enteritis there is an extremely marked *fall of blood pressure.* This is *almost entirely vascular in origin;* for if the aorta is clamped, the heart is able to maintain a fairly high pressure (Boehm and Unterberger, 1874). This vascular paralysis is *mainly peripheral,* but it differs from that produced by the nitrites, for stimulation of the peripheral stump of the splanchnic nerve is still effective in raising the blood pressure, at least in the earlier stages. The arterioles must therefore still be capable of contracting. For this reason it is assumed that structures beyond the arterioles — namely, *the capillaries — are the seat of the paralysis.* This view is favored by the fact that they have become more permeable. (Intravenous injections of large quantities of salt solution will cause edema in animals poisoned with As, but not in the normal.) There is in addition a weakening of the heart, and probably also some depression of the vasomotor center and partial paralysis of the arterioles. All these contribute to the fall of pressure.

These changes in the capillaries explain practically the whole course of the poisoning. Since *increased permeability* of the capillaries is one of the essential features of inflammation, one need not be surprised that the phenomena of arsenic-poisoning are similar to those produced by an irritating inflammation, although the primal cause is different.

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[1] Exercises 32 and 67.

[2] The principal use which is now made of this corrosive action is in killing the nerves of teeth. This takes several days, which illustrates the slowness of the corrosive action, and contrasts very strikingly with the extremely rapid onset of the symptoms in acute poisoning.

The first and strongest effects are upon the *intestine*, no matter how the arsenic has been introduced. The capillary paralysis results in the production of an exudation into the connective tissue. This raises the epithelium (just as would a blister on the skin), and causes it to be thrown off in shreds or false membranes. The exudation is then poured into the lumen of the intestine and largely coagulates. This distention, as well as the circulatory changes, causes increased peristalsis and *watery diarrhea;* and the shreds of mucus and coagulated exudation give to the evacuations the character of *"rice water" stools* (Boehm and Pistorius, 1882).

The pathology of this condition is exactly the same as that of Asiatic cholera, and without a history it is absolutely impossible to distinguish between the two conditions except by chemic examination of the dejections.

The extreme distention of the capillaries may lead to their rupture, to the formation of ecchymoses, or possibly bleeding into the intestine or stomach, and consequently bloody vomiting or diarrhea; but this is by no means always the case.

The vessels of the kidneys also participate in the dilation. The glomerular capillaries are swollen so as to fill the capsule; the urine is albuminous and scanty, and cannot be increased by caffein (Hellin and Spiro, 1897).

The great distention of the splanchnic area will of course withdraw a great amount of blood from the general circulation, and this will react upon other organs. In some cases this effect is so violent that it produces collapse, from paralysis of the central nervous system, before the symptoms of enteritis have had time to develop. This corresponds exactly to "dry cholera."

Death usually occurs by exhaustion as a result of the prolonged gastro-enteritis, as in cholera. There are the same muscle cramps, paleness, and general collapse. The patient appears emaciated from the withdrawal of liquid from the body by the profuse diarrhea, and this even if he retains a fair amount of adipose tissue.

2. Chronic Arsenic-poisoning.— With a still less acute action a *chronic gastro-intestinal catarrh* is developed, possibly with ulceration. The less intense but persistent capillary paralysis will give time for the development of more pronounced *degenerative changes* in other parts of the body. Most prominent amongst these are fatty degenerations, first of the *endothelium* of the capillaries themselves. Later this affects the *intestinal epithelium*, and finally the cells of other organs — *liver, kidney, heart muscle*, etc. This is due to the interference with nutrition. The increased size of the liver from the fatty degeneration may cause pressure on the bile ducts, consequently reabsorption of bile and icterus. In the chronic action of arsenic there is quite a tendency to the development of *local effusions*. Amongst the first of these is *swelling of the eyelids*, which is fairly characteristic.

The impaired nutrition of the nerve-trunks gives rise to *polyneuritis*, with atrophy of the muscles, disturbance and paralysis of sensation, and also of the special senses. The *voice* is very frequently altered, from paralysis of the vocal cords. The *skin* is also particularly subject to the action of arsenic, perhaps because it takes part in its excretion. This action results in acne-like eruptions, exfoliation, and in falling out of hair and detachment of finger-nails. In a few cases a peculiar cutaneous *melanosis* can be noticed. This is not due to a deposition of arsenic, but to the formation of an organic pigment. The mucous membranes, especially the conjunctivæ, may also suffer.

3. Beneficial Action on Metabolism.— If the doses of arsenic are small, this capillary dilatation and hyperemia may not reach a harmful degree, and may even lead to an increased nutrition. This deserves especial attention, since it is the rational basis of the use of arsenic in the various cachetic conditions. The metabolic action is quite variable, as it depends upon a number of mutually opposed causes. Amongst these are: the capillary dilatation; supposedly a direct action of arsenic upon the cells; and the action upon the gastro-intestinal canal and upon the kidneys.

The interaction of these factors may produce very different results. Consequently the experimental data are not of very much value. It may be considered as proven, however, that as long as the arsenic does not interfere with digestion and absorption, it *increases* the *excretion of nitrogen*. If this interference is avoided, arsenic also causes *increased deposition of fat*. Another effect which is found in arsenic-poisoning is the loss of the glycogen of the liver and formation of sarcolactic acid.[1] What practical importance can be attributed to this is not at present clear. The diminution of glycogen is so rapid that it cannot be ascribed to a diminished power of forming it. Nor does it seem to be connected with the lactic acid formation.

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[1] Other poisons which cause diminution of glycogen are: Phosphorus, mercuric chlorid, chloroform, colchicin, strychnin, and nitrobenzol.

One of the therapeutic uses of arsenic is to *increase the number of erythrocytes*. There seems to be considerable evidence that it does so in certain forms of anemia, by stimulating the bone-marrow. It has no such effect in normal animals. In normal animals, small repeated doses of arsenic affect the *bone-marrow* by causing atrophy of the fat-cells, dilation of capillaries, and increase of leucoblastic (not erythroblastic) cells. Pb, P, Hg, etc., produce the same changes. Large doses cause hyaline degeneration, and lessen the erythrocytes and hemoglobin of the blood. Arsenic also leads to *thickening of the bones* and filling up of the Haversian canals, which may possibly justify its use in rickets (Gies, 1877).

On the whole, there can be no doubt that in some cases the early use of arsenic *increases the rate of growth and weight* of the animal; in detail, causing an increase in nitrogen metabolism and a deposition of fat and an increased strength of the bones. The nutrition of the *skin* is also said to be especially improved by it.

It is used quite largely in veterinary practice to give the coats of horses and cattle a bright appearance. Its use to improve the complexion is not rare. The people of certain countries — the mountainous districts of Silesia — use it to secure an *improvement in general health*. There appears to be unimpeachable evidence that they gradually accustom themselves to use with immunity quantities of arsenic (to 0.4 Gm.) which would produce very serious toxic, irritant and cumulative effects in ordinary individuals (Schaefer, 1861; Knappe, 1875). Some tolerance to the fatal action probably exists also, but is not so very large. This *acquired immunity* is the more strange since it has never been attained with animals (Hausmann, 1903). The fact that the corrosive action of other metals can to a large extent be lost by habituation is perhaps suggestive, but it is impossible to say whether the two phenomena are connected.

III. ABSORPTION AND EXCRETION.

Arsenic is very readily **absorbed,** even from the unbroken skin. Quite a number of cases of poisoning have occurred in this way from the use of arsenical cosmetic preparations. When it is injected subcutaneously the diarrhea often sets in within an hour.

It is **excreted** by all the excretions — urine, feces, sweat, milk, and epithelium of the skin (Heffter, 1905).

The excretion begins in 2 to 8 hours after the administration, but lasts for a long time — 3 to 10 days, after a single dose; to 70 days when it had been given continuously. In rabbits' urine it was found for 120 days, in dogs' for 160 days, after the administration was stopped. It is stored in all organs; not especially in the liver, as was at one time claimed. It also passes across the placental circulation to the fetus. It is just as toxic when injected into the mesenteric, as by the jugular vein, showing that the liver neither neutralizes nor retains it. It is less toxic on hypodermic injection, since it enters into more slowly dissociated compounds with the tissue elements.

A very small amount of arsenic is often normally present in certain human organs, notably in the thyroid (0.16 mg.); also in the thymus, brain, and skin. It appears to be tied to the nuclein. None is found in the liver.

This arsenic is introduced with the food and especially the drinking water. (According to the Royal Commission, 1903, the quantity of arsenic in food should not exceed $^{1}/_{100}$ grain per pound, or in liquids, per gallon.)

The quantity of arsenic normally present in the intestinal canal *never* exceeds $^{1}/_{10}$ mg. Larger quantities point to poisoning (Gautier, 1904).

Lower Animals.—Arsenic is toxic to all animals which possess a central nervous system; also to most of the higher plants, but not to all the lower organisms. Its antiseptic action is comparatively small. It cannot therefore be classed as a general protoplasmic poison.

Plants and cold-blood animals resist arsenates much better than arsenites, whilst warm-blooded animals do not show this difference. It is probable that the arsenite ion is the more toxic, the tissues of warm-blooded animals reducing arsenates to arsenites. New-born salamanders show a very great tolerance.

IV. TOXICOLOGY.

The main interest of arsenic lies in its toxicology.

1. **Etiology.**—Arsenic was at one time used very extensively for criminal poisoning, especially in the seventeenth century. An Italian woman, Toffania, carried this science to its greatest refinement, using under the name of "Acqua Toffana" a mixture of arsenic and ptomains obtained from the putrefied juices of animals poisoned with arsenic.

At the present time arsenic is rarely used with criminal intent, the most frequent forms of poisoning being suicidal or accidental. This may be attributed to the perfection of the chemic means of detection, which allow of the discovery of the minutest trace.[1] Accidental poisoning has been lessened to some extent by requiring the preparations of arsenic sold at retail to be colored either with lamp-black or indigo, so that they do not have the innocent appearance of a white powder. This is also of some importance in diagnosing the poisoning, the color of the vomit calling attention to it. But accidental and suicidal poisoning is still very common, since arsenic is so extensively distributed. It is easy to obtain it as a rat and fly poison. It is frequently used in the arts. Paris green is a preparation whose sale is almost unrestricted. A great many of the cosmetic preparations on the market contain arsenic and have given rise to accidents. The use of arsenic compounds, such as Schweinfurth green, as *pigments* has been absolutely prohibited; but a great many of the *coal-tar dyes*, which are popular at the present time, employ arsenic in their preparation, and very frequently this is not entirely removed. Formerly *wall-paper* dyed with arsenic compounds was a common source of arsenic poisoning, but this has now practically disappeared.

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[1] A very delicate biologic test has recently been announced, depending upon the development of a garlic-like odor, when the mold Penicillium brevicaule is grown upon an arsenical medium. Quantities as small as $\frac{1}{300}$ to $\frac{1}{500}$ mg. of arsenious acid could be demonstrated by its acid (Gosio, Scholz, 1899).

The arsenic is given off from these papers as dust. However, undoubted cases of poisoning have also occurred when the arsenical paper was completely covered by a harmless paper; in these, some volatile arsenic compound must be formed.

The permissible limit of arsenic in papers is placed at 0.1 grain per square yard; but this is probably not quite harmless. The Bureau of Chemistry of the United States Department of Agriculture has analyzed a number of papers on the American market (Haywood and Warner, 1904). Over 90% of these contained less than 0.046 grain per square yard, and are therefore safe. *Furs, rugs, and fabrics* were less satisfactory. *Black stockings* particularly often contained quantities of arsenic (above 0.01 grain per square yard), which must be considered dangerous, considering their intimate contact with the skin.

The **fatal dose** of arsenic is upward of a decigram.

The **course** of arsenic-poisoning may be very quick. There is a fulminant type in which death is almost immediate. The usual course, however, takes from eighteen to seventy-two hours. In some cases it may take much longer — from four to fourteen days.

2. The **symptoms** have been sufficiently discussed, but will bear recapitulation. In **acute poisoning** there may be a sudden collapse without other symptoms. Usually, however, the symptoms do not appear for from one-half to one hour after the arsenic is taken. The suspicion of the patient may have been aroused by the sweetish astringent taste of the substance. Almost the first symptoms are vomiting and profuse and painful diarrhea. The withdrawal of water from the body leads to great thirst, dryness of the mouth and throat, and difficulty in swallowing and articulation. The urine is diminished and often bloody. The excretion of the arsenic through the kidneys will pro-

duce a nephritis. On the part of the central nervous system there are vertigo, headache, and pain in the limbs. There will be cyanosis and cold extremities. Toward the end occur syncope, coma, clonic and tonic spasms, and a general paralysis.

In the **subacute poisoning** the inflammation of the mucous membrane of the alimentary canal will form a still more prominent symptom. Inflammation of other mucous membranes also becomes conspicuous, and shows as conjunctivitis, coryza, stomatitis, salivation, and pharyngitis. Skin eruptions make their appearance if the arsenic-poisoning is at all prolonged. In this case there are also symptoms arising from the central nervous system, as well as neurites.

The **diagnosis of acute arsenic-poisoning** is made by the violent gastro-enteritis. This can usually be distinguished quite easily from that produced by acids and alkalies, by the history of the case, absence of corrosion in the mouth, and furthermore by the lesser prominence of the local symptoms. The very quick onset distinguishes it from other metals.

The **diagnosis of chronic arsenic-poisoning** may be somewhat difficult because the symptoms are sometimes quite obscure or resemble very closely those produced by chronic lead-poisoning. There is some difference in the electric reaction of muscle and the absence of the blue line on the gums, which are characteristic of lead. But in other cases of the acute or chronic form the chemic examination is the only absolute means of making the diagnosis.

3. In the **postmortem examination** there would be a very pronounced dryness of the tissues. The emaciated appearance of the body, even with a fair amount of adipose tissue, the appearance of the alimentary canal with its large amount of fluid and the presence of shreds of mucus and false membrane, with usually no pronounced corrosion, are characteristic.[1] Microscopically gastro-adenitis and cell infiltration are often seen. The body after arsenic-poisoning usually putrefies very slowly and may become mummified, which always causes a suspicion, although it is not at all a proof of such poisoning. The positive proof can only be furnished by the chemic examination. It must not be for-

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[1] See plates 49 and 50 of E. v. Hofmann: Atlas of Legal Medicine, W. B. Saunders Co.

gotten that arsenic is frequently introduced into the body in the embalming fluid.

4. Treatment of Arsenic-poisoning.— Acute arsenic-poisoning is best treated by emetics through lavage with warm water, or purgation. *Ferri Hydroxidum cum Magnesii Oxido* (see Index) was long considered the best antidote, the ferric hydrate and iron forming a compound which was deemed almost insoluble. De Buscher[2] believes, however, that the compound is even more soluble than arsenous acid, and that it is quite ineffective. So also is hydrogen sulphid.

Chronic arsenic poisoning is treated by withdrawing the cause; the same measure may also be used as for chronic lead poisoning (see index).

V. THERAPEUTICS.

As to the therapeutics of arsenic, it has some *local uses* which will be discussed among the caustics. Its **systemic action** is used for the improvement of nutrition in various cachetic conditions. Although it is easily understood how it may be of benefit in these cases, its actual use must be entirely empirical. We do not know sufficient about the nature of these conditions, nor can we predict the action of arsenic with sufficient certainty, to be able to foretell its results. It is usually worthy of a trial in such cachetic conditions as malaria, pernicious anemia, etc. In chlorosis it seems to aid the iron preparations, but does not act alone. Its use in rickets has been alluded to (p. 612). It has been used in chorea (rapidly increasing doses), phthisis, and asthma, but clinicians disagree as to its value, and there is no scientific basis for its employment.

In its **administration,** it should be aimed to establish a tolerance by beginning with small doses, and gradually increasing these until some local manifestation of the arsenic appears — usually diarrhea or conjunctivitis or swelling of the eyelids. As soon as these are seen, the amount must be diminished.

VI. MATERIA MEDICA OF ARSENIC.

Solid Preparations:

Arseni Trioxidum (U. S. P.) [*Acidum Arseniosum,* B. P.].— (Arsenous Acid, Arsenic Trioxid, White Arsenic.) — A_2O_3. White powder, or glassy, or porcelain-like masses. Odorless and tasteless. Slowly soluble in 30 (glassy) or 100 (powdered or porcelain) parts of water; in 15 boiling water; sparingly in alcohol. Freely soluble in hydrochloric acid and alkalies. *Dose:* 1 to 6 mg. ($^1/_{60}$ to $^1/_{10}$ gr.) (2 mg. = $^1/_{30}$ gr., U. S. P.).

Sodii Arsenas (U. S. P.).— $Na_2HAsO_4 + 7H_2O$. Soluble in 1.2 water, sparingly in alcohol. *Dose,* as for the preceding (5 mg. = $^1/_{10}$ gr., U. S. P.).

Sodii Arsenas Exsiccatus (U. S. P.).— Na_2HAsO_4. Soluble in 3 water. *Dose,* as the preceding (3 mg. = $^1/_{20}$ gr., U. S. P.).

Arseni Iodidum (U. S. P., B. P.).— AsI_3. Orange red powder. Soluble in 12 water (partial decomposition), 28 alcohol. *Dose,* as the preceding (5 mg. = $^1/_{10}$ gr., U. S. P.).

* *Ferri Arsenas.*— Insoluble. *Dose:* 0.001 to 0.006 Gm. ($^1/_{60}$ to $^1/_{10}$ grain).

Liquid Preparations.— All contain 1% of the arsenic preparation and have the *dose* of 0.12 to 0.6 c. c. (2 to 10 minims) (0.2 c. c. = 3 ♏, U. S. P.).

Liq. Acidi Arsenosi (U. S. P.) [*Liq. Arsenii Hydrochlorici,* B. P.].— Contains 0.5% HCl.

Liq. Potassii Arsenitis (U. S. P.) [*Liq. Arsenicalis,* B. P.].— (*Fowler's Solution.*)— Flavored with Tinct. Lavand. Co.

Liq. Sodii Arsenatis (U. S. P., B. P.).

Liq. Arseni et Hydrargyri Iodidi (U. S. P., B. P.).— (*Donovan's Solution.*) — Contains 1% of each (0.1 c. c. = 1½ ♏, U. S. P.).

* *Sodium Cacodylate.*— $(CH_3)_2As.O(ONa)$. The arsenic in this compound, as also in cacodylic acid and cacodyl oxid, does not exist as ion, and does not therefore produce the arsenic action directly. The greater part is excreted unchanged by the urine, but a small proportion is converted into arsenous acid, and acts as such (Schulz, 1879). These compounds are therefore much less toxic than arsenic, but have also correspondingly smaller therapeutic actions. Whatever advantages they possess — and clinicians are still at variance as to the superiority over ordinary arsenic — must be due to the slow liberation of the arsenic (Heffter, 1901). Since this occurs readily in the stomach, the cacodylate should by preference be used hypodermically or intravenously. The hypodermic *dose* of sodium cacodylate is 0.05 to 0.2 Gm. (1 to 3 grains) per day. It is a white, crystalline, odorless, and tasteless salt, quite soluble in water.

VII. SELENIUM AND TELLURIUM.

Selenium and Tellurium resemble arsenic in the general action on the capillaries of the splanchnic area. They also affect the central nervous system, apparently directly. Tellurates arrest perspiration (after the manner of atropin?), and have been recommended for this purpose; but they impart a very persistent garlic odor to the breath, tissues, urine, and feces, even in a quantity as small as 0.005 mg.! This may last for several months after the administration is stopped. It is caused by methyl-tellurid. Selenium is more toxic than tellurium (Woodruff and Gies, 1902).

* *Sodii Telluras.*— Na_2TeO_4.— *Dose:* 0.016 to 0.05 Gm. (¼ to ¾ grain).

Vanadium.— According to Luzzato (1903) poisonous doses of VCl_3 or VBr_3 cause the usual anatomic lesions of metals in the kidneys, liver, intestine, and stomach. No lesions are found in the central nervous system. The blood pressure is raised, and the excitability of the vagus is depressed. Death occurs through respiratory paralysis. Vana-

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*** Not official.**

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dium is said to act as an alterative, somewhat like arsenic, increasing the hemoglobin and red blood cells. It has therefore been recommended in tuberculosis. It has also been used in diabetes, with the claim that it reduces the excretion of sugar to a half. The statement needs confirmation.

* *Lithii Vanadas.—Dose:* 4 to 5 mg. (1/15 to 1/12 grain) per day.

* *Sodii Meta-vanadas.*—White, almost tasteless powder, soluble in water. *Dose:* 1 to 8 mg. (1/60 to 1/8 grain). According to Jardin (1905), it lessens assimilation and increases proteid destruction.

* *Vanadium Chlorid* or *Bromid.—Dose* to 30 mg. (1/2 grain) per day.

IV. ANTIMONY.

1. The **actions** of antimony bear a close resemblance to those of arsenic. The difference lies in a greater local irritation and a much lesser absorption. Consequently, *when given by the mouth,* doses can be chosen whose only action is that of producing nausea, or if somewhat larger, vomiting.[1] If *injected into the circulation,* or if given in overdoses, it produces precisely the same effects as arsenic, but vomiting is always a prominent phenomenon, the poison being rapidly excreted into the alimentary canal. Small doses long continued lead to a train of symptoms of *subacute poisoning,* entirely analogous to those produced by arsenic in the same manner (Gaehtgens, 1876; Soloweitschyk, 1880).

The **treatment** consists in giving eggs, milk, and tannin (tea, etc.), or in its absence magnesia.

Applied to the skin, the chlorid is a strong caustic. The double tartrate of antimony and potash (tartar emetic) produces a pustular eruption. This is due to the decomposition of the double salt, which is but slightly irritant, by the acid secretion of the follicles into more irritant simple salts.

2. Therapeutically the tartar emetic is the salt most frequently employed *internally.* As an *emetic* it has fallen out of favor, its action being too slow and too depressing. As a *nauseant* it has advantages over all other metals, since the dose required for this is only about one-tenth of that which produces vomiting. The sulphid is preferred by some, since this dissolves much more slowly, and therefore has a more lasting action. Antimony preparations are useful as diaphoretics and expectorants (see pp. 312 and 518).

For *local uses* see Chapter XXVIII.

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* Not official.

[1] Exercise 30.

MATERIA MEDICA OF ANTIMONY.

Solid Preparations:

Antimonium Nigrum Purificatum (B. P.).—*Sulphid* (Trisulphid) *of Antimony* (*Black Antimony*).—Sb_2S_3. The native sulphid, purified by washing with ammonia water. Insoluble black powder. Used only in the preparation of the other compounds.

Antimonium Sulphuratum (B. P.).—(*Kermes Mineral.*)—Consists chiefly of Sb_2S_3 with a small amount of Sb_2O_3. Made by dissolving Sb_2S_3 in NaOH and precipitating with H_2SO_4. Insoluble reddish powder. *Dose:* 0.01 to 0.06 Gm. (1/6 to 1 grain).

This is contained in:

Pilulæ Antimonii Compositæ (*Plummer's Pill*):

Each pill contains:

	GRAMS.	GRAINS.
Sulphurated Antimony	0.04	2/3
Calomel	0.04	2/3
Guaiac	0.08	1 1/3

Dose: 1 to 3.

Antimonii Oxidum (B. P.).—Sb_2O_3. A gray powder obtained by precipitating antimony chlorid with water, and treating with Na_2CO_3. *Dose:* 0.06 to 0.24 Gm. (1 to 4 grains).

Antimonii et Potassii Tartras (U. S. P.) [*Antimonium Tartaratum*, B. P.].—*Tartar Emetic* (*Tartarus Stibiatus*).—$2K(SbO)C_4H_4O_6 + H_2O$. White crystals or powder, prepared by treating Sb_2O_3 with acid potassium tartrate. Soluble in 15.5 parts water, insoluble in alcohol. *Dose:* 0.006 to 0.03 Gm. (1/10 to 1/2 grain) for Expectorant and Diaphoretic (5 mg. = 1/10 gr., U. S. P.); 0.06 to 0.12 Gm. (1 to 2 grains) for Emetic (30 mg. = 1/2 gr., U. S. P.).

Liquid Preparations:

Vinum Antimonii (U. S. P.) [*Vinum Antimoniale*, B. P.].—0.4% Tartar Emetic (℥j = gr. ij). *Dose:* Expectorant, 0.3 to 2 c.c (5 to 30 minims) (1 c.c. = 15 ♏, U. S. P.); Emetic, 4 to 15 c.c. (ʒj to iv).

Syrupus Scillæ Compositus (U. S. P.) (*Hive Syrup*):

Contains:	In 100 c.c.:	In ʒj:	In 2 c.c.:
Squills	8.0 Gm.	4 grains.	0.16 Gm.
Senega	8.0 "	4 "	0.16 "
Tartar Emetic..	0.2 "	1/8 grain.	0.004 Gm.

Used especially in whooping cough. *Dose:* 0.3 to 2 c.c. (5 to 30 minims) (2 c.c. = 30 ♏, U. S. P.).

V. URANIUM.

This is one of the most poisonous of metals. The uranium salts are very corrosive, and are in consequence readily absorbed from the alimentary canal. Their action resembles that of arsenic, but in addition they lessen internal respiration after the manner of hydrocyanic acid.

The symptoms of poisoning include a severe gastro-enteritis, with ecchymoses. Degeneration of the walls of blood-vessels and of organs occurs. There is a strong nephritis; the amount and specific gravity

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of the urine are increased, and it contains sugar and albumin. The glycosuria is probably an expression of the "internal asphyxia."

The metal has *no therapeutic indications.*

* *Uranium Nitrate.*— $UO_2(NO_3)_2$, Soluble.

VI. BISMUTH.

If *a soluble bismuth salt* is injected directly into the blood, it produces the arsenic phenomena on blood-vessels. There is perhaps also a direct involvment of the central nervous system and depression of the vasomotor center. The heart-muscle is also depressed. The blood pressure sinks, therefore, very rapidly (Meyer and Steinfeld, 1885).

Bismuth forms a black and very insoluble sulphid. Since H_2S is always present in the large intestine, the feces are always colored black. When the bismuth is in the blood, the precipitation may occur in the vessels of the large intestine, and lead to capillary embolism, and this to ulceration. Therapeutically, the avidity for H_2S serves to remove this irritant from the intestinal canal, and the benefits of bismuth may be due to this, in certain cases.

Soluble bismuth salts are also quite *corrosive.*

These toxic effects may be produced by comparatively small doses of soluble bismuth salts, taken by the mouth; the bismuth being absorbed in virtue of its corrosive action. The intact intestinal mucosa does not absorb bismuth to any considerable degree, so that the small amount which is brought into solution by the gastric juice when the insoluble basic salts are given, is quite harmless. These basic bismuth compounds may, however, be absorbed in sufficient quantity to *produce poisoning, if they are applied to extensive wound surfaces.* The soluble bismuth salts have no therapeutic use: they lack entirely the qualities which make the basic salts so valuable.

Basic (Oxy) Bismuth Salts.— These occur as very fine powders, absolutely insoluble in water, and very sparingly soluble in the body fluids. They have a marked healing effect when dusted on wounds and on inflamed mucous surfaces. Applied to wounds, they cause a drying of the secretions and form a protective covering, so that the wound heals as under an aseptic scab. This action is partly mechanical, due to the stoppage of the lymph- and blood-capillaries by the fine particles of the powder. Other indifferent substances in an equally fine state of subdivision have a similar action. However, a small amount of bismuth undoubtedly goes into solution, and aids by exerting an astringent and mild antiseptic action. The subnitrate of bismuth especially is used as a dusting powder or, as in the case of the urethra, by injecting a suspension in thin mucilage. In the alimentary canal, the basic bismuth salts act not only in the manner indicated, but also by neutralizing excessive acidity and by precipitating hydrogen sulphid. The combination of these actions makes these preparations, either the subnitrate or subcarbonate, very useful for checking diarrhea, and sometimes against vomiting. If there is excessive intestinal putrefaction, they are best given in conjunction with an intestinal antiseptic, such as salol.

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* Not official.

Various substitutes have been proposed for the established subnitrate and subcarbonate, but it may be doubted whether they have any advantage.

The subgallate (*Dermatol*) and other basic organic salts, as also the albuminate and peptonate, have been introduced as dusting powders. In view of the non-corrosive character of the ordinary subnitrate, it is difficult to see in what they could be superior. An iodized product of the subgallate is marketed under the name of *Airol;* the iodin may perhaps increase the antiseptic power somewhat.

There is rather more reason for the products in which the bismuth is combined with phenols. The latter are split off in the intestine, and act there as efficient antiseptics. These compounds (with *phenol*), tribromphenol (*xeroform*), with betanaphthol (*orphol*), etc.) are therefore especially useful against putrefactive diarrheas; but it is doubtful whether they have much advantage over simple mixtures of the subnitrate with intestinal antiseptics (*salol*).

MATERIA MEDICA.

1. **Insoluble Salts.**— *Dose:* 0.3 to 2 Gm. (5 to 30 grains). (White powders, tasteless, and odorless.) Incompatible with acids and alkalies.

Bismuthi Subcarbonas (U. S. P., B. P.).— $(BiO)_2CO_3 + xH_2O$. Prepared by pouring a solution of $Bi(NO_3)_3$ into Na_2CO_3 (0.5 Gm. = 7½ grs., U. S. P.).

Bismuthi Subnitras (U. S. P., B. P.).— $BiONO_3 + xH_2O$. Prepared by pouring a solution of $Bi(NO_3)_3$ into water (0.5 Gm. = 7½ grs., U. S. P.).

Bismuthi Citras (U. S. P.).— $BiC_6H_5O_7$. Treating bismuth subnitrate with citric acid (0.125 Gm. = 2 grs., U. S. P.).

Bismuthi Subgallas (U. S. P.).— (*Dermatol.*)— Yellow powder. 0.25 Gm. = 4 grs., U. S. P.

Bismuthi Subsalicylas (U. S. P.) [*Bismuthi Salicylas*, B. P.].— 0.25 Gm. = 4 grs., U. S. P.

The * *insoluble organic compounds* of bismuth (*Airol, Phenol-Bismuth, Orphol, Xeroform,* etc.) are tasteless and odorless powders. Those intended for internal use are given in *doses* of 0.3 to 1. Gms. (5 to 15 grains) per day.

2. **Soluble Bismuth Salts and Their Preparations.**— The value of bismuth preparations lies precisely in their sparing solubility, so that the following are not scientific:

Bismuthi et Ammonii Citras (U. S.).— Bismuth Citrate dissolved in Ammonia and dried to scales. Very soluble in water, sparingly in alcohol. *Dose:* 0.12 to 0.3 Gm. (2 to 5 grains).

* *Elixir Bismuthi* (N. F.).— 3.5% Citrate of Bismuth and Ammonia.

Liquor Bismuthi et Ammonii Citratis (B. P.).— *Dose:* 2 to 4 c.c. (½ to 1 drachm).

*** Not official.**
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VII. IRON.

I. SUMMARY OF ACTIONS.

1. An increased formation of *hemoglobin,* resulting in improved *nutrition,* produced in certain forms of anemia, but not in normal individuals.
2. An increase of the *reserve stock of iron* in the body.
3. A *local* astringent, styptic, irritant, or corrosive action.

4. An *arsenic-action* when the salts are *injected intravenously* (preparations which do not precipitate the serum proteids) or subcutaneously; or when corrosive preparations are introduced in the alimentary canal. When iron is suddenly introduced into the circulation in this manner, it is almost as toxic as arsenic (Jacobj, 1887). In medicinal doses, iron is not absorbed in sufficient amount to show this action, even in the slightest degree.

II. THE ABSORPTION, EXCRETION, AND METABOLISM OF IRON.

The investigations of Tartakowski (1903 and 1904) have settled several disputed questions in this subject, and necessitate a revision of the theories which prevailed when the first edition of this book was published. The absorption and assimilation of iron has been one of the great "Streitfragen" of pharmacology, which deserves to be studied as illustrating the general course of investigating a difficult problem, as well as for its practical bearing.

All compounds of iron, when introduced in the alimentary canal, are first converted into loose organic compounds (probably with proteids), in which form they are absorbed from the entire surface of the intestinal canal, but particularly from the duodenum. A part generally escapes absorption and is eliminated with the feces. The part which is absorbed penetrates the epithelium in a dissolved condition, and passes through the stroma into the lacteals, and from here to the mesenteric lymph glands and through the thoracic duct into the blood. In the lymph, the iron exists partly in solution in the plasma, and partly in the lymph corpuscles, often in granule form (ferrocytes). It is probable that a part of the iron is also absorbed by the capillaries and carried directly to the liver. From the blood, the iron is deposited as granules in an easily decomposed organic form (ferratin) in the cells of the hematopoetic organs, in the liver and red marrow, and particularly in the spleen, to a less extent in the kidneys. In this form it remains until it is used or excreted. The excretion is not perfectly understood, but it occurs mainly by the cells of the intestinal tract, as a firm organic compound. Traces are also excreted in the urine, bile and gastric juice.

The utilization of the iron, its transformation into hemoglobin, occurs only as needed, so that the total quantity of hemoglobin never rises above normal. The same is probably true of its utilization by other cells. An excessive absorption of iron results merely in an increase of the reserve stock.

The administration of iron is therefore useful only in those conditions in which the normal income or the assimilation of iron are deficient.

There is at present no conclusive evidence that different forms of iron have a different fate in the body; the indications are rather that they behave exactly alike.

Organic and Inorganic Iron.—To understand the discussion one must have a clear conception of the terms "inorganic" and "organic" iron. *Inorganic iron preparations* contain the metal in ion-form; *i. e.*, the iron can be separated from them by electrolysis; and they give the ordinary iron reactions (with ammonium sulphid, ferrocyanid, or hemotoxylin) without preliminary treatment of any kind. It is immaterial whether the iron is combined with an organic or inorganic anion. Even the albuminate of iron is considered as "inorganic" in this sense. *Organic iron preparations*, on the other hand, contain the metal as a constituent part of the molecule, in a non-dissociable condition, so that they do not give the iron tests until the metal has been liberated by the decomposition of this molecule. There are all degrees in the firmness of the organic combination: some are decomposed by dilute acids (ferratin, the granules in which the iron reserve is stored in the spleen, liver, etc.); in others (hemoglobin, and the iron of food) nothing short of combustion or heating with concentrated acids will liberate the iron.

Historical Summary.— Even the ancients employed iron in the treatment of anemia; drinking water in which swords had been allowed to rust. It is very likely that they were led to do so by an obscure idea that the strength of the steel would in some way pass into the patient. With the discovery of the presence of iron in the blood, the therapeutic results seemed to be easily explained on the assumption that the iron is absorbed and converted into blood, much as the nitrogen of food is converted into muscle. The earlier experiments, however, failed to show any absorption of the medicinal iron preparations. This led some observers to consider the clinical results obtained with iron as largely imaginary; whilst others (especially Bunge, 1885) were inclined to attribute them to the local actions of iron on the alimentary canal.

There could never be any question as to the absorption of food-iron, for the hemoglobin increases with the growth of the animal. The same holds true for certain organic irons, and MacCallum (1894) and Hall (1896) studied this absorption by microchemic methods. The absorption of inorganic iron was also proven, but the latter result was criticized, the objection being made that the iron had produced corrosion. This was finally withdrawn, but it was now claimed that inorganic iron, whilst it is absorbed, cannot be converted into hemoglobin (Abderhalden, 1899; Hoffmann, 1900); but that it is nevertheless beneficial in anemia, by stimulating the blood-producing organs to a better use of the organic irons.

These misconceptions were due to difficulties inherent in the problem, which could only be gradually overcome.

Estimation of Iron in the Excreta.— If one wishes to show the absorption of nitrogen or of chlorids, it suffices to estimate the quantity of these substances in the food, and in the feces and urine. The same method was applied to iron. The results seemed to show that absolutely no absorption occurs, for the iron of the feces approximates that of the food, and the iron in the urine is not at all increased. It was soon shown, however, that the intestines are the principal channel for the excretion of the iron; for the feces contained this metal even in starvation; and when iron was injected subcutaneously very much more was excreted by the feces than by the urine. It was therefore evidently impossible to decide whether the fecal iron was unabsorbed or excreted. Absorption could only be proven, by this method, if it predominated greatly over the excretion. The estimation of the iron in the bile and in the intestinal juice gave similarly inconclusive results.

Estimation of Iron in the Body and in Organs.— A much more promising method of investigation consists in the estimation of the iron in the tissues. Since it is necessary to kill the animal in order to estimate the iron, it was necessary to make control-experiments. This would be impossible if the animals were chosen at random, for the individual differences of iron content are often greater than the quantities which could be absorbed. Bunge found, however, that the proportion of iron in new-born animals is very high, and that it decreases steadily during the period of lactation (because milk is very poor in iron) until it has reached a practically constant quantity — about the 17th day in guinea-pigs or rabbits, and the 23d or 24th day in dogs. The animals of the same litter can therefore be used for controls, some being fed, at the end of the lactation period, with iron-poor food, others with the same food to which the iron preparation is added. Rice and milk, which contain a very small proportion of iron, are commonly employed. The animals which do not receive the iron thrive very poorly, remaining small and emaciated. Those which receive iron, in any form, show an unmistakable increase in the total iron content of the body, especially of the liver and spleen (Hall, 1894). But to obtain differences beyond the experimental error, it is necessary to administer fairly large quantities. These are of course especially exaggerated when small animals, such as mice or rats, are used; this exposed the earlier experiments to the very reasonable charge that the inorganic iron preparations were absorbed merely because of their corrosive action (Häussermann). This has only recently been disproved by using larger animals, in which it can be definitely shown that there is no such corrosion.

Microchemic Method.— Important information was obtained by applying the color reactions for iron directly to the tissues. The macroscopic examination of the depth of stain gives a general idea of the quantitative distribution of the iron, the details being revealed by microscopic study. Since, however, the iron compounds are apt to dissolve in the fixing solutions, many of the earlier experiments gave fallacious results. The best method consists in hardening the tissues in alcoholic ammonium sulphid and converting the ferrous sulphid into the more stable Berlin blue, by treatment with potassic ferrocyanid and dilute hydrochloric acid. Only the inorganic and the loosely combined organic iron is revealed.

The experiments are made on animals with different diets, or fed on iron, for varying periods. The absorption of the iron, and its deposition in the hematopoetic organs can be followed in this way, eading to the conclusions detailed on page 622.

Reserve Stock of Iron.— Animals on an ordinary diet lay up a considerable reserve stock of iron, as loose proteid compounds, especially in the spleen. This reserve disappears gradually when a diet poor in iron is given, or when there is an extraordinary use of iron, as after hemorrhages, or during pregnancy (when considerable iron is transferred to the fetus). The deposits increase, on the other hand, when the iron of the food is increased. If the lymph is made to flow off through a fistula of the thoracic duct, the increase of the iron content of the spleen does not take place (Gaule, 1896); this, together with the increased iron content of the mesenteric lymph glands, indicates that the iron is largely absorbed through the lymphatic system. (The "liver" of mollusks also accumulates a stock of iron.)

Excretion of Iron.— The chemical data have proven that iron is excreted principally by the cells of the alimentary canal. The cells of the *large intestine* show a particularly strong iron reaction, granules occurring especially toward the fundus of the crypts. This was supposed to indicate that the iron was in process of excretion, especially since the reaction could be obtained for a considerable time in starvation. It has been shown, however, that the reaction fails when the access of food is prevented (by a Thiry fistula). The scanty secretion which occurs in this isolated segment does, however, give an iron reaction after incineration. This forces to the conclusion that the iron is excreted in very firm organic combination; and that the loosely bound iron in the cells of the large intestine is really in process of absorption. It is not known whether any of the excreted iron can be reabsorbed, or whether the iron which is liberated during the destruction of red corpuscles can be utilized again; the impossibility of producing severe anemia in adult animals by limiting the iron of the food, *indicates that the iron-stock may be used several times*. But a considerable portion is undoubtedly lost by the feces.

Assimilation of Iron.— It would be quite conceivable that the absorbed iron, particularly the inorganic preparations, were of as little use to the organism as the particles of solid carbon which are absorbed by the lungs. It had to be shown, therefore, that the iron can be actually assimilated and converted into hemoglobin. This could not be done on normal animals, because the normal income of iron is amply sufficient for all the needs of the organism; an excess has no effect whatever on the hemoglobin. The animals must be reduced to a condition in which the needs exceed the ordinary income. In young and actively growing animals, this may be secured by a diet poor in iron (milk and rice). This produces a progressive fall of the percentage of hemoglobin, and the animals become emaciated and do not develop. As soon as iron, in any form, is added to the diet, the animals recover very rapidly. It must therefore be concluded that all forms of iron can be assimilated. The same result is obtained with adult animals. These cannot be rendered markedly anemic by an iron-poor diet; by drawing on their reserve stock, and possibly by utilizing the iron several times, they can keep up an almost normal percentage of hemoglobin for a considerable period. They can, however, be rendered anemic by hemorrhage. Even a rather severe single hemorrhage is rapidly recovered from on a milk and rice diet; but when several hemorrhages have been made and the iron reserve has become exhausted, recovery occurs only when iron (in any form) is added to this diet.

Does Inorganic Iron Stimulate the Bone Marrow? — The earlier experiments seemed to indicate that inorganic iron only increased the hemoglobin when it was given in conjunction with organic iron; it was therefore assumed that it could not be assimilated, but that it stimulated the blood forming organs. The above experiments remove the need for this theory, which has no longer any experimental foundation.

Synthesis of Hemoglobin.— The conversion of iron into hemoglobin is perhaps the only known instance of the synthesis of a proteid from a strictly inorganic compound, in the animal organism.

Local Actions of Iron on the Alimentary Canal.— The inorganic salts of iron produce an astringent effect, which may conceivably support their other actions, by improving digestion. There is always danger, however, that the useful action passes into irritation, and, in fact, iron causes digestive disturbance (especially constipation) more often than improvement. It may be useful in fixing sulphuretted hydrogen when this is present.

The administration of iron *does not cause renal irritation.*

Effects on General Nutrition.— Whilst these are doubtless mainly the indirect result of the increase of hemoglobin, it must not be overlooked that iron forms a constituent of most cells, and some of its effects may be direct; but its importance in this connection is difficult to estimate. The majority of organisms require some iron, even those which do not form hemoglobin. (The blood of some *invertebrate animals* contains copper or manganese in place of iron.)

III. THERAPEUTICS OF IRON.

1. In Anemia.— The administration of iron would be useful in all conditions in which the need for iron exceeds its income; conditions which are characterized by a low percentage of hemoglobin, and by the general clinical picture of anemia.

It does not follow, however, that iron will be beneficial in every case of anemia; on the contrary, it is to be expected that it will be useless when the assimilation, rather than the increase of iron, is deficient. In **pernicious anemia,** for instance, a most severe destruction of corpuscles is accompanied by a conspicuous increase of the reserve-iron of the spleen. A further supply of iron would be valueless, as has been confirmed by clinical experience.

The plainest indication for iron is furnished by the anemia produced by severe or repeated **hemorrhage. Infantile anemias** are often traceable directly to a deficient iron content of the food, and would be greatly benefited by iron.[1] Some cases of simple anemias in adults may also be due to this cause.

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[1] This will be the case especially when the infant is kept too long on an exclusive milk diet. It may also be favored by an inferior quality of milk: whilst normal human milk contains 3.5 to 7.2 mg. of iron per liter (mean

Most instances of anemia, and especially **chlorosis,** cannot e attributed directly to deficient iron-income; but neverheless, the administration of iron secures very brilliant esults. It must therefore be supposed that conditions xist in these diseases, which demand an extraordinary ncome of iron to keep the hemoglobin normal.

Iron in Chlorosis.— A complete explanation of the action of iron in hlorosis can only be furnished when the *pathology* is understood. This is not the case at present; little is known beyond the fact that he hemoglobin is decreased much more than the number of corpuscles, and that the excretion of iron by the urine is nearly normal.[1] Even the question, whether the reserve stock of iron is altered, does not seem to be decided. Digestive disturbances are often present, but they may be secondary or accidental.

Our knowledge of the *etiology* is equally unsatisfactory. It has indeed been shown by Stockmann that the diet of chlorotic girls is often very poor in iron (containing 2.8 to 3.2 mg. per day, instead of the normal, 6 to 14 mg.). But this, as well as other unhygienic conditions, can only be considered as contributory factors, since many persons are subject to these conditions, whilst chlorosis is confined to females about the age of puberty.

The *treatment* is much more successful than might be expected. The administration of iron holds the first place. This should be supplemented by proper hygiene — good air, rest, suitable diet, stomachics, attention to the bowels (aloes), etc. Arsenic, phosphorus or manganese are often used in addition to the iron: it is difficult to judge of their value.

Administration.— The objects to be kept in mind are: to administer a maximum of iron, with a minimum of digestive disturbance. The latter object can be best met by food-iron or organic iron. However, it is impossible to introduce large quantities of iron by the food; and the organic iron preparations (hemoglobin, ferratin, iron-somatose, etc.) are rather expensive. Of the inorganic iron preparations, the least irritant are: reduced iron (as powder or pills), and the carbonate or sulphate (as pills). Ferric chlorid (tincture) is generally given when a fluid form is desired. The incompatibilities of iron, especially with tannin, must be remembered.

The dose is to be regulated by the experience in each case. When it is badly born, a change to another prepara-

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5 mg), that of unhealthy mothers is poorer in iron; and artificial infant foods generally contain only 1.4 to 2.6 mg. It is conceivable that deficiencies in the iron-income are concerned in the etiology of rickets and the other nutritive diseases of infants.

[1] A table of the iron in the blood and urine, in various diseases, is given on p. 620 of the first edition of this book. The iron of the urine amounts normally to about 1 mg per day. It is slightly increased in fever, nephrites, hepatic disease, leucemia and especialy in diabetes.

tion is sometimes useful. The tendency to constipation must be met by aloes or other cathartics.

Iron Content of Food.— It suffices to remember that blood, meat, yolk of eggs, and the green portions of vegetables are especially rich in iron (17 to 40 mg. per 100 Gm. of dry substance); whilst egg white, milk, and the cereals (especially white flour) are poor in iron. Whole wheat, potatoes and the legumes are intermediate.[1]

2. Local Uses of Iron.— The tincture of ferric chlorid is employed as an astringent, especially in gargles (1:10); this, and particularly the Liq. Ferri Subsulph., are also used as local styptics.

IV. MATERIA MEDICA OF IRON.

Only the most important preparations need to be studied. It may be remembered that ferric salts have a reddish, ferrous a greenish color. The most important *incompatibilities* are: alkalies, tannin, salicylates, phenol.

1. Preparations Used Mainly Externally:

Ferri Chloridum (U. S. P.).— $FeCl_3 + 6H_2O$. Freely soluble in water or alcohol. 22% Fe. *Dose:* 0.065 Gm. = 1 gr. (U. S. P.).

Liquor Ferri Chloridi (U. S. P.) = about 29% of the anhydrous salt, or 10% Fe. *Dose:* 0.1 c. c. = 1½ ♏ (U. S. P.).

Liquor Ferri Perchloridi Fortis (B. P.) = 22½% Fe.

Liquor Ferri Nitratis (B. P.) = 3.3% Fe.

Liquor Ferri Subsulphatis (U. S. P.) (*Monsel's Solution*, made by oxidizing Fe_2SO_4 with HNO_3 and H_2SO_4) = 13.6% Fe.

Liquor Ferri Tersulphatis (U. S. P., B. P.) (*Solution of Ferric Sulphate*) = about 36% of $Fe_2(SO_4)_3$ = 10% Fe.

This is used in the preparation of:

Ferri Hydroxidum Hydratum cum Magnesii Oxido (U. S. P.) (*Arsenic Antidote*).

The following should be kept on hand:

A: Liquor Ferri Tersulphatis 40, Water 125.
B: Magnesia 10, Water 800.

When wanted, B is well shaken, A is added, and the mixture is shaken until smooth. It is given in tablespoonful doses, very frequently repeated (in all 125 c. c. = 4 ℥), and followed by lavage or emetic, and a saline purgative.

2. Insoluble Inorganic Preparations (administered as powders or pills):

Ferrum (U. S. P.).— Bright wire, used in making the salts.

Ferrum Reductum (U. S. P., B. P.).— By reduction of ferric oxid by hydrogen. *Dose:* 0.06 to 0.3 Gm. (1 to 5 grains) (0.065 Gm. = 1 gr., U. S. P.).

Trochiscus Ferri Reducti (B. P.).— Each contains 1 grain.

Ferri Carbonas Saccharatus (U. S. P., B. P.).— 15% $FeCO_3$. Made by precipitating $FeSO_4$ with $NaHCO_3$. Greenish-brown powder of sweetish ferruginous taste; easily oxidized in air. *Dose:* 0.12 to 0.6 Gm. (2 to 10 grains) (0.25 Gm. = 4 grs., U. S. P.).

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[1] A table of the iron-content of food is given on p. 621 of the first edition of this book.

Ferrous Carbonate is also contained in:

Massa Ferri Carbonatis (U. S. P.).—(*Vallet's Mass.*)—Used in pill form. *Dose:* 0.06 to 0.3 Gm. (1 to 5 grains) (0.25 Gm. = 4 grs., U. S. P.).

Pilulæ Ferri Carbonatis (U. S. P.) [*Pilula Ferri,* B. P.].—[*Blaud's* (*Chalybeate*) *Pills.*] *Dose:* 1 or 2 (5 to 10 grains, B. P.).

Ferri Hydroxidum (U. S. P.).—(*Ferric Hydrate.*)—$Fe(OH)_3$. Made by precipitating Ferric Sulphate with Ammonia. Used in the preparation of other salts.

Ferri Phorphos (B. P.).—*Dose:* 0.3 to 0.6 Gm. (5 to 10 grains).

3. Solid Soluble Inorganic Salts: Administered in pill-form or solution. Generally insoluble in alcohol, unless otherwise stated.

FERROUS SALTS.

		Solubility in Water.	Per Ct. Metallic Iron.	Average Dose (U. S. P.).
Ferri Sulphas (U. S. P., B. P.) *Ferri Sulphas Granulatus* (U. S. P.)	$FeSO_4 + 7H_2O$..	0.9	......	0.2 Gm. = 3 grs.
Ferri Sulphas Exsiccatus (U.S.P.).—100 Gm. dried to 65 Gm.....		......	......	0.125 Gm. = 2 grs.
Pilulæ Aloes et Ferri (U.S.P.). *Dose:* 2 pills = 0.14 Gm. = 2 grs. of ferrous sulphate and aloes.				
Pilulæ Ferri Iodidi (U.S.P..—*Dose:* 2 pills = 0.08 Gm. Fe and 0.10 Gm. iodin.				

FERRIC SALTS, CRYSTALS.

Ferri Chloridum.—See above.			
Ferri et Ammonii Sulphas (U.S.P.).—*Ferric Alum.*—$FeNH_4(SO_4)_2 + 12H_2O$. Violet crystals	2.7	11.5	0.5 Gm. = 7½ grs.
Ferri Hypophosphis (U.S.P.).—$Fe(PH_2O_2)_3$	2300	......	0.2 Gm. = 3 grs.

FERRIC "SCALE" SALTS, SIMPLE.

The "scale salts" occur as thin, transparent scales, of somewhat uncertain composition. They have a garnet-red to reddish-brown color, with the exception of Sol. Iron and Quinin Citrate, Sol. Phosphate, and Pyrophosphate, which are green:

	Solubility in Water.	Per Ct. Metallic Iron.	Average Dose (U. S. P.).
Ferri Citras[1] (U.S.P.)..........	Sol.	16.	0.25 Gm. = 4 grs.
Ferri Phosphas Solubilis (U.S.P.)	Freely sol.	12.	" "
Ferri Pyrophosphas Sol. (U.S.P.)	" "	10.	" "

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[1] A 10% solution of this salt has been used for administering iron subcutaneously (Dose: 1 c. c.). The results are fairly good, but the injections are rather painful. Overdoses cause gastric irritability.

DOUBLE SALTS.

	SOLUBILITY IN WATER.	PER CT. METALLIC IRON.	AVERAGE DOSE (U. S. P.).
Ferri et Ammonii Citras (U.S.P., B.P.)	Freely sol.	16.	0.25 Gm. = 4 grs.
Ferri et Ammonii Tartras (U.S.P.)	" "	13.	" "
Ferri et Potassii Tartras (U.S.P.) (Ferrum Tartratrum, B.P.)..	Very sol.	15.	" "
Ferri et Quininæ Citras (U.S.P., B.P.) (11.5% quinin)........	Slowly sol.	13.5	" "
Ferri et Quininæ Citras Solubilis (U.S.P., B.P.) (11.5% quinin.)......	Quickly sol.	13.5	" "
Ferri et Strychninæ Citras (U.S.P.) (1% strychnin)....	Freely sol.	16.	0.125 Gm. = 2 grs.

The **Proteid Salts of Iron* [*Albuminate* (5% Fe); Peptonate, 0.25%; Caseinate, etc.] are given as powders. *Dose:* 1 Gm. = 15 grs.

4. Liquid Inorganic Iron Preparations, Simple:

The liquid preparations of iron have a very injurious effect upon the teeth if brought in contact with them. They should therefore be taken through a glass tube, and the mouth rinsed thoroughly.

	AVERAGE DOSE (U.S.P.).	
Syrupus Ferri Iodidi (U.S.P., B.P.), 5% FeI_2	1 c. c. = 15 ♏.	
Tinctura Ferri Chloridi (U.S.P.), 13.28% of $FeCl_3$ (to be largely diluted)	0.5 c. c. = 8 ♏.	
Liquor Ferri et Ammonii Acetatis (U.S.P.) (*Basham's Mixture*).......	16 c. c. = 4 ʒ.	
Liquor Ferri Acetatis (B.P.) (to be largely diluted)	0.12 to 0.6 c. c.	2 to 10 min.
**Ferrum Dialysatum*, a 10% aqueous solution of ferric oxychlorid, freed from excess of HCl by dialysis (to be largely diluted)	0.6 to 2.0 c. c.	10 to 30 min.
**Elixir Ferri Phosphatis* (N.F.), 3.5% Ferric Phosphate	2 to 4 c. c.	30 to 60 min.
Liquor Ferri Perchloridi (B.P.) and *Tinctura Ferri Perchloridi* (B.P.)... (Each contains one-fourth of the stronger solution.)	0.3 to 1 c. c.	5 to 15 min.
Syrupus Ferri Phosphatis (B.P.) (1 drachm = 1 grain)	4 to 8 c. c.	1 to 2 drachms.
Vinum Ferri (U.S.P., B.P.) (Iron and Amm. Citr., 4%)....................	8 c. c. = 2 ʒ.	

* Not official.

5. Liquid Inorganic Iron Preparations, Compound:

	Dose: C.c.	Dose: Drachms.
Mistura Ferri Composita (U.S.P., B.P.) (*Griffith's Mixture*). About 0.7% of Ferrous Carbonate in suspension in flavored water..	16	4
Syrupus Ferri Phosphatis cum Quinina et Strychnina (B.P.) (*Easton's Syrup*).......	2 to 4	½ to 1
Ferric Phosphate 2%		
Quinin Phosphate 3%		
Strychnin 0.02%		
Elixir Ferri, Quininæ, et Strychninæ Phosphatum (U.S.P.) (see Index).............	4	1
Glyceritum Ferri, Quininæ, et Strychninæ Phosphatum (U.S.P.) (see Index).............	1	¼
Vinum Ferri Amarum (U.S.P) (Iron and Quinin Citrate, 5%, flavored with orange)..	8	4
Syrupus Hypophosphitum Compositus (U.S.P.)	8	2

6. Iron (Chalybeate) Mineral Waters.— These contain the iron most often as ferric bicarbonate; sometimes as sulphate, oxid, and very rarely as chlorid.

7. Organic Iron Preparations.— Only some of the scientific preparations can be considered in this connection. *None are official.* The *dose* is usually 1 Gm.

(a) Artificial Preparations:[1]

	Percentage of Iron.
Ferratin (ferri-albuminic acid): Originally prepared from liver (Schmiedeberg, 1894), but at present obtained artificially (Marfori, 1892). Insoluble...	6.0
Iron Somatose (albumose): 2% Fe. Soluble......	15.

Ferri vitellinum Syntheticum (Ovoferrin); combination of ferric hydrate with modified serum-albumin. *Dose* of 5% solution = tablespoonful, = 0.065 Gm. (1 grain) Fe.

(b) From Blood:

Blood, in its original form, is too repellant to be therapeutically useful. Its character may be disguised by *drying,* or by mixing it with glycerin. Pure *hemoglobin* and *hematin* are too expensive; a sufficiently pure form of hematin may be prepared cheaply by digesting blood with an acid pepsin solution: the hematin is precipitated, whilst the other proteids remain for the most part in solution, and can be removed by washing. (Sollmann, 1902).

Hemols: Obtained by the reduction of hemoglobin through zinc dust (or by other metals)..........	0.2% Fe.
Hemogallol: Obtained by precipitating blood by pyrogallol	

(c) From Other Sources:

Hematogen (Bunge, 1885): A nucleo-proteid from egg yolk	0.3% Fe.

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* No official.

[1] Geisse, 1898, describes the behavior of these compounds to MacCallum's iron reaction.

Various other nucleo-proteids are also used, such as *Ferratogen,* obtained by the artificial digestion of yeast grown on media containing iron; =1% Fe.

VIII. MANGANESE AND CHROMIUM.

Manganese and chromium are not absorbed in sufficient amount to have any general action, the phenomena in poisoning by the soluble salts (permanganates, chromates, etc.) being entirely local; *i. e.,* exerted upon intestines and kidneys. This holds true even when the soluble preparations are introduced into the circulation.

The chromium salts cause a diabetes. This is due purely to injury of the kidney, for the sugar of the blood does not rise above normal if the .ureters are ligated. The *nephritis* is confined mainly to the tubular epithelium (Gergens, 1876). When bichromates are given by the mouth, they are reduced to chromous oxid and partly deposited as such in very numerous organs, the rest being excreted by the urine (Kappeler, 1896).

The *absorption and excretion of manganese* is the same as that of iron (see pp. 622 to 626) (Harnack and Schreiber, 1901).

Manganese dioxid is sometimes used empirically as an emmenagogue, or to replace iron in its other uses, but is of very questionable utility.

	SOLUBILITY IN WATER.	AVERAGE DOSE. (U.S.P.)
Mangani Dioxidum Præcipitatum (U.S.P.), MnO_2	Insol.	0.25 Gm. = 4 grs.
Mangani Sulphas (U.S.P.), $MnSO_4 + 4H_2O$	0.7	0.25 Gm. = 4 grs.
Mangani Hypophospis (U. S. P.), $Mn(PH_2O_2)_2 + H_2O$	......	0.2 Gm. = 3 grs.
Potassii Permanganas (U. S. P., B.P.), $KMnO_4$	15	0.065 Gm. = 1 gr.
**Syrupus Ferri et Mangani Iodidi* (N.F.)	......	4 to 8 = 1 to 2 drachms.
Chromii Trioxidum (U.S.P., B.P), CrO_3	Very sol.	Only externally.
Potassii Dichromas (U.S.P., B.P.), K_2CrO_7	9	10 mg. = 1/5 gr.
Liquor Acidi Chromici (B.P), 25%	......	Only externally.

IX. ALUMINUM.

The salts of this metal have a purely local action when given by the mouth; they are not at all absorbed from the intact alimentary canal (Plagge and Lebbin, 1893). Even very large doses cause only a local exudative inflammation (hence vomiting and diarrhea). This is due to their precipitating proteids. They are therefore antiseptic and astringent. The precipitate is, however, soluble in an excess of proteid. They spread very slowly even when injected subcutaneously, and appear to penetrate cells with the greatest difficulty; for the symptoms appear only several days or weeks after the injection (Siem, 1886), at a time when the metal has entirely disappeared from the blood, and has become fixed in the cells. The symptoms then resemble those of subacute arsenic-poisoning. They never occur when aluminum salts are given by mouth, no matter in what doses, nor how long continued.

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* Not official.

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The quantities which may be dissolved from aluminum cooking vessels, even by dilute acids, are too small to be of any importance. The same is true of residues of alum baking powders (see below).

The *therapeutic importance* of aluminum salts lies exclusively in their local astringent action.

		DOSE:	
ONE PART DISSOLVES IN	WATER:	Metric.	Apothecaries'.
Alumen (U.S.P., B.P.), *Alum*. $AlK(SO_4)_2 + 12H_2O$. (For external use see gargles, injections, eye-waters, etc., 2%; for tonsilitis, 20% glycerite as paint)................	9	0.03 to 2.0 (0.5 Gm. = 7½ grs., U.S.P.)	5 to 30 grs.
Alumen Exsiccatum (U.S.P.), *Burnt Alum*. (Alum from which the water of crystallization has been expelled by roasting.) Used locally in powder form as styptic......	17		
Alumini Hydroxidum (U.S.P.), $Al(OH)_3$. By precipitating alum with Na_2CO_3.....................	Insol.	0.06 to 0.6	1 to 10 grs.
Alumini Sulphas (U.S.P.), $Al_2(SO_4)_3 + 16H_2O$.......................	1		
**Alumnol* (Beta-naphthol-disulfonate of aluminum). Antiseptic astringent; 1 to 5% aq. solution, or as dusting-powder (mixed with 5 to 10 parts starch or talcum)........			
Glycerinum Aluminis (B.P.), 10%..			

Baking Powders.—These are chemicals which serve as substitutes for yeast-fermentation, aerating bread and pastry dough by evolving carbonic acid. They are of course altered in this process. The decomposition products are partly expelled by the heat of baking. The fixed residue is the part which could conceivably produce pharmacologic action.

The baking powders belong to four chemic types (Crampton, 1889):

1. *Cream of Tartar Powders.*— Mixture of acid potassium tartrate and sodium bicarbonate. Reaction: $KHC_4H_4O_6 + NaHCO_3 = KNaC_4H_4O_6 + CO_2 + H_2O$. Residuum: 11 Gm. of Rochelle Salts per loaf of bread. Innocuous.

2. *Phosphate Powders.*— Calcium super-phosphate and sodium bicarbonate. Reaction: $CaH_4(PO_4)_2 + 2NaHCO_3 = CaHPO_4 + Na_2HPO_4$

* Not official.

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$+ 2CO_2 + H_2O$. Soluble residuum: 3.5 Gm. sodium phosphate per loaf of bread. Innocuous.

3. *Alum Powders.*— Alum (usually ammonic) and sodium bicarbonate. Reaction: $(NH_4)_2Al_2(SO_4)_4 + 6NaHCO_3 = Al_2(OH)_6 + 3Na_2SO_4 + (NH_4)_2SO_4 + 6CO_2$. Residuum, per loaf of bread: 1.3 Gm. aluminum hydrate; 3.65 Gm. sodium sulphate; 1.1 Gm. ammonium sulphate. The aluminum hydrate is insoluble in water; in the stomach, a trifle may be dissolved by the hydrochloric acid, and perhaps by the proteids; but so little that it cannot be important. The sulphates are practically without action. (The addition of alum whitens pastry baked from inferior flour. This fraudulent use is prohibited in several countries.)

4. *Ammonium Carbonate.*— Decomposed and volatilized as $NH_3 + CO_2$. Expelled so completely that it is inactive.

Some baking powders are mixtures of several of the above. They are often diluted with indifferent substances (starch, etc.).

X. CERIUM AND THORIUM.

The actions of these metals is evidently closely related to those of aluminum. *Cerium* is used, as the insoluble oxalate, against vomiting, especially in pregnancy (Simpson, 1854; Mills, 1876). This action is purely local and probably analogous to that of bismuth. It is unlikely that any cerium is absorbed. The systemic actions of the soluble salts have not been adequately studied.

Cerii Oxalas (U. S. P., B. P.).— $Ce(C_2O_4)_3 + 9H_2O$. (Cerous oxalate.) — Contains also other earths (didymium, lanthanum, etc.). White, odorless and tasteless powder; permanent in the air; insoluble in water or alcohol; soluble in dilute acids. *Dose:* 0.05 to 0.5 Gm. (1 to 8 grains) (0.065 Gm. = 1 gr., U. S. P.).

* *Cerium Nitrate* (soluble) has been substituted, in doses of 0.05 Gm. or less.

Thorium.— The nitrate of thorium is markedly astringent, precipitating proteids and coagulating blood. Injected hypodermically, it causes ulceration. The toxicity is slight. It is fairly well tolerated by the stomach, very large doses being required to produce vomiting. It is not absorbed from the alimentary canal. The addition of sodium citrate prevents the coagulant action. When this solution is injected intravenously, it has absolutely no effect on the circulation, or any other function, even when 0.25 Gm. are injected per Kilogram of dog. However, the animals remain emaciated, and show ulcers of the gums. When killed, after some weeks, an extensive calcification of connective tissue is noticed. The thorium is excreted by the kidneys. The solutions have no effect on the excised muscle or heart of frogs (Chace and Gies, Brown and Sollmann, 1905). The nitrate was tried for stimulating ulcers, but did not prove superior to alum. The oxalate and oxid are practically insoluble.

Neodymium, Praesodymium and Lanthanum (as the chlorids) also precipitate proteids, and the observed effects can be attributed to this reaction (antisepsis, paralysis of muscle, etc.) (Dreyfuss and Wolf, 1905).

XI. COBALT AND NICKEL.

These metals are only absorbed when given in strongest solutions or when long continued. The local action is that of metals in general, with nothing particularly characteristic. Nickel salts have been used as emetics, but are not to be recommended.

When introduced into the circulation they affect the central nervous system directly, in addition to the usual metal action on capillaries, heart, and kidneys. There are tremors, chorea, and convulsions, followed by paresis. In frogs the medulla is stimulated before the spinal cord (A. Stuart, 1884).

The urine is increased, and always contains sugar, often proteids. Cobalt salts act as antidotes to HCN poisoning, through the formation of cobalt-cyanids. To be effective they must be introduced subcutaneously in doses which are not devoid of danger. They are therefore not to be used in man.

* *Niccoli Bromidum.*— Freely soluble. *Dose:* 0.13 to 0.52 Gm. (2 to 8 grains).

XII. SILVER.

This metal is absorbed in extremely small amount, and is reduced to the inactive metallic state as soon as it enters the body (Jacobi). For this reason it can never lead to general poisoning, and the only evidence of its absorption lies in a dark discoloration (argyrism) of the skin and certain situations, after its prolonged administration. This is due to the deposition of metallic silver in the connective tissue of the corium, the sweat glands, in smooth muscle, villi of intestine, etc. (Frommann, 1859; Riemer, 1876). It is not seen in most animals.

If the silver is introduced into the circulation its effects differ from those of other metals in the predominance of nervous symptoms. These are central and mainly paralytic. There is motor paralysis beginning in the hind legs, depression of the respiratory center with asphyxial convulsions, stimulation of the vasoconstrictor center, followed by paralysis, etc. The secretion of bronchial mucus is so greatly increased that it may lead to asphyxia. This is probably due to injury to the epithelium (Ball, 1865; Jacobi, 1877).

The *therapeutic employment* of silver in insanity, etc., is a survival of the fantastic teaching of the middle ages, when it was based on its dedication to the moon, and the supposed connection of the latter with lunacy. Although it is absolutely proved that silver cannot be absorbed in amounts sufficient to have any action whatsoever, it has been tried again and again against all forms of nervous disease, with uniformly negative results. The indications for it are purely local.

Silver is one of the most toxic metals for bacteria and protozoa, but is comparatively innocuous for the mammalian organism. The salts have a great affinity for proteids, and are therefore astringent, irritant, or caustic, according to the strength in which they are used.

This combination of astringent, caustic, and antiseptic actions, and the ease with which the effect may be graduated, make the silver salts, particularly the nitrate, very valuable. The lactate has recently been introduced under the name of "*actol*," but seems to possess no advantage. The citrate (also known as "*itrol*") may be used sparingly as a dusting-powder, since it is so little soluble (requiring 4,000 parts of water) that it cannot become caustic.

The ordinary silver salts do not penetrate very deeply, since they are precipitated by proteids and chlorids. The addition of diethylendiamin to silver phosphate prevents this precipitation. This compound (*Argentamin*) is therefore more penetrating. It is marketed as a fluid containing as much Ag as a 10% silver nitrate solution, and is used in corresponding strengths.

The precipitation can also be avoided by *combining the silver with proteids*. The resulting products usually dissolve slowly in cold water. The solutions decompose on exposure to light. A number of these products are on the market, such as *Argyrol* (with vitellin, 20 to 25% Ag.); *Argonin* (with casein, 4% Ag.); *Protargol* (with albumose, 8% Ag.); *Largin* (with protalbin, 11% Ag.). The compounds retain the bactericidal properties of silver, but are practically non-astringent and non-irritant. The absence of these qualities may be desirable in some cases, whilst it is a serious drawback in others. They are used in gonorrhea (1/10 to 2%); conjunctivitis (0.5 to 5%); nose and throat infections (2 to 10%); etc.

Colloidal Silver ("Collargolum") is also permanently soluble in albuminous fluids, but is rendered insoluble by excessive quantities of salts. It is claimed to possess a peculiar value, since it is itself inert and harmless, and remains so in contact with normal tissues; whilst bacteria transform it into the active ionic form. It should therefore act automatically. It has been used locally like the ordinary silver salts; subcutaneously, in 0.5% solution for tuberculous joints; and systemically for septicemia. For the latter purpose it may be given by mouth (pills of 0.01 Gm.); by inunction (3 Gm. of *Unguentum Crédé* (15%) per day; or intravenously (10 c. c. of 0.5%).

	SOLUBILITY IN WATER.	DOSE: Metric.	DOSE: Apothecaries'.
Argenti Nitras (U.S.P., B.P.), *Silver Nitrate* (Lunar Caustic), $AgNO_3$ .... If given internally, it is best made into pills with clay and vaselin. Externally in 1/5% to 2% solution. (See eye-waters, injections, ulcers, etc.)	0.54	0.015 to 0.06	1/4 to 1 gr. (10 mg. = 1/6 gr., U.S.P.)
Argenti Nitras Fusus . (U.S.P.) (Lunar Caustic in sticks). Contains a small quantity of chlorid.			
Argenti Nitras Induratus (B. P.). Contains 5% of KNO_3 and fused into rods			
Argenti Nitras Mitigatus (U.S.P., B.P.) (*Mitigated Caustic*). Made by fusing 3 parts $AgNO_3$ and 6 parts KNO_3, pencils.			
Argenti Oxidum, Ag_2O (U.S.P., B.P.)	Insol.	0.03 to 0.12	1/2 to 2 grs. (0.065 Gm. = 1 gr., U.S.P.).

XIII. GOLD AND PLATINUM.

Gold and platinum are still more easily reduced to the metallic state than is silver, and are therefore devoid of general action when taken by the mouth. When injected into the circulation they produce an arsenic action. They should have no place in rational therapeutics. (Gold, Schultz, 1892; Platinum, Kebler, 1878; Cohnstein, 1892).

Auri et Sodii Chloridum (U. S. P.).—Equal parts of gold chlorid ($AuCl_3$) and NaCl. *Dose:* 0.002 to 0.006 Gm. (1/30 to 1/10 grain) (5 mg. = 1/12 gr., U.S.P.).

[*] *Liq. Auri et Arsenii Bromidi* (N. F.).—*Dose:* 0.06 to 0.5 c. c (1 to 8 minims).

Gold Tribromid	0.325%
Arsenic Tribromid	0.65%

XIV. TIN.

This metal is absorbed in part even from non-corrosive preparations. But poisoning is very rare, the metal not passing very easily into soluble form, and having no pronounced tendency to cumulative action. The symptoms on injection devolve to some extent on the central nervous system, as stimulation and subsequent paralysis. The arsenic action and paresis of heart are also prominent. With more chronic poisoning the gastro-enteritis is most marked, but there is also an ataxia and motor paralysis, resembling chronic lead-poisoning (White, 1880).

XV. COPPER, ZINC, AND CADMIUM.

These metals are closely related in their action. Given by the mouth, copper and zinc salts have a rather specific irritant action, affecting at first exclusively the nerve structures which form the starting-point of the *vomiting* reflex. In consequence, vomiting occurs before there is time for corrosion, and relatively large doses present no danger. Nor is there any danger of chronic poisoning. This is of some importance on account of the use of copper to give a green color to preserved *vegetables*. These contain 0.20 to 0.50 mg. of Cu per kilogram. It is, of course, conceivable that copper salts may become deleterious through their continued local action, but the quantities introduced with these vegetables may be affirmed to have no such effects. The slight traces remaining in water after purification by copper (see page 382)[1] are probably equally harmless. Quantities of the copper sulphate up to 0.5 Gm. per day have

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[*] Not official.

[1] The latest investigators (Clark and Gage, 1906) assign a very limited value to the copper treatment of water.

been shown to be devoid of bad effects (Du Moulin). It is true that these were not continued indefinitely.

The local irritation by Cu and Zn causes these to be used as emetics (see p. 315).[1] The nausea is too short to allow of their use as expectorants. They are also used as astringents and mild caustics.

If *introduced into the circulation* they cause death through paralysis of the cardiac muscle. They also affect the central nervous system, probably directly, especially Zinc and Cadmium. The effects are mainly paralytic. The brain is affected first — *i. e.,* consciousness is lost,— but the motor areas are not involved. The blood pressure falls rapidly, but this is mainly due to the cardiac depression.

Copper depresses the excised skeletal muscles, whilst Cadmium (and probably Zinc) has little action upon them.

Zinc Oxid has been used *therapeutically* against epilepsy. Its usefulness is doubtful, but not disproved.

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The copper and zinc salts are used *locally;* the soluble salts in concentrations of ½ to 10%; the insoluble zinc compounds as ointments (5 to 20%). When used *internally* the soluble salts should be well diluted.

SOLUBLE SALTS.

One Part is Soluble in	Water.	Alcohol.	Average Dose. (U.S.P.).
Cupri Sulphas (U.S.P., B.P.). —*Blue Vitriol, Bluestone.* $CuSO_4 + 5H_2O$	2.2	400	Astringent: 10 mg. = ⅙ gr. Emetic: 0.25 Gm. = 4 grs., repeated if necessary.
Zinci Acetas (U.S.P., B.P.).— $Zn(C_2H_3O_2)_2 + 2H_2O$	2.5	36.	0.125 Gm. = 2 grs.
Zinci Bromidum (U.S.P.).— $ZnBr_2$	Readily	Readily	0.125 Gm. = 2 grs.
Zinci Chloridum (U.S.P., B.P.).— $ZnCl_2$	0.4	Readily	....
Zinci Iodidum (U.S.P.).— ZnI_2	Readily	Readily	0.065 Gm. = 1 gr.
Zinci Phenolsulphonas (U.S.P.), *Zinci Sulphocarbolas* (B.P.) $Zn(C_6H_5O_4S)_2 + 8H_2O$	1.7	1.7	0.125 Gm. = 2 grs.
Zinci Sulphas (U.S.P., B.P.). —*White Vitriol.* $ZnSO_4 + 7H_2O$	0.53	in sol.	Emetic: 1 Gm. = 15 grs.

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[1] Exercise 30.

		ONE PART IS SOLUBLE IN WATER.	ALCOHOL	AVERAGE DOSE. (U. S. P.)
Zinci Valeras (U.S.P.) *Zinci Valerianas* (B.P.)	$Zn(C_5H_9O_2)_2 + 2H_2O$.	50.	35.	0.125 Gm. = 2 grs.

Zinc Bromid, Chlorid, and Iodid are *very deliquescent,* whilst Zinc Acetate, Phenolsulphonate, Sulphate, and Copper Sulphates are *efflorescent.*

Liquor Zinci Chloridi (U.S.P., B.P.).— 50%. Strongly caustic.

INSOLUBLE ZINC COMPOUNDS.

Amorphous, white powders.

Zinci Carbonas Præcipitatus (U. S. P.) [*Zinci Carbonas,* B. P.].— A hydrated carbonate, yielding not less than 72% ZnO.

Zinci Oxidum (U.S.P., B.P.).— ZnO. *Dose:* 0.25 Gm. = 4 grs., U. S. P.

Zinci Stearas (U. S. P.).

Zincum (U.S.P.).

ZINC OINTMENTS.

Unguentum Zinci Oxidi (U. S. P.).— 20%, in benzoinated lard.

Unguentum Zinci (B. P.).— 15% of the oxid.

Unguentum Zinci Stearatis (U.S.P.).— 50% in white petrolatum.

Unguentum Zinci Oleatis (B.P.).

XVI. MERCURY.

I. ACTION.

Mercury, unlike the other metals, has a strong specific *toxic action on protoplasm.* It is poisonous not only to the higher plants and animals, but also to lower organisms, and possesses great germicidal power. It owes this toxicity to a great affinity for nitrogenous molecules.

1. **Absorption.**— The albuminates which are formed in this manner are quite soluble under the conditions of the body — *i. e.,* if a certain amount of sodium chlorid and of alkalinity exists. In consequence, it is *readily absorbed* and transported, differing very conspicuously from other metals in this respect. Further, whilst most metals are almost innocuous in the free state, *metallic mercury* is fairly toxic; its distribution and absorption are favored by the fact that it is liquid and volatile and oxidizes very readily.

The mercury compounds are absorbed from all surfaces. On this rest the mercurial treatments by fumigation and inhalation. Many cases of mercury-poisoning have also

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occurred from flushing out large cavities with mercuric solutions. The absorption from serous surfaces is very rapid.

2. The **excretion** of mercury occurs to some extent by the urine, but mainly by the intestine; also to some degree by saliva, sweat, and milk. The excretion by the kidneys begins in about two hours after the administration, but it lasts for a long time, and may be demonstrated for eight days after a single dose, and for as late as six months after the administration has been entirely stopped, after continued use.

With small amounts this excretion causes no pathologic changes in the kidneys; but if long continued it gives rise to interstitial and glomerular nephritis.[1] Large amounts, on the other hand, occasion a parenchymatous nephritis with glycosuria. The relative quantity of mercury excreted by this channel is increased by the inflammatory changes.

Potassium iodid is said to favor the excretion, just as in the case of lead, but there is not much positive evidence on this point. It is equally doubtful whether the excretion can be hastened by diuresis.

3. **Fate in Body.**— Whilst the elimination of mercury is a slow process, it disappears quite rapidly from the blood, being fixed in the tissues.

Its distribution is much the same as that of lead. It is found especially in the kidneys, to a less extent in the liver, and frequently in the intestinal walls. When taken as vapor it is also found in the lungs. In other organs it is seen only in acute poisoning. It passes through the placenta only when given in very large doses, probably after injuring the vessels. The mercury which has been stored is quite firmly fixed in the non-digestible nuclein residue, favoring the view that it is deposited in the nuclei.

When injected directly into the blood-vessels the organic (non-ion) mercury preparations act more violently than the inorganic. Although mercury, like other metals, does not act until it has been converted into ion form, the organic compounds are distributed more quickly throughout the body and are readily decomposed.

II. TOXICOLOGY.

1. **Etiology.**— The most frequent cause of mercury-poisoning was formerly the excessive and *injudicious medicinal use* of this metal. The mercury existing in the amalgam used for filling teeth seems to be so firmly com-

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[1] Exercise 33.

bined that it does not cause poisoning. The chances for *accidental chronic poisoning* with mercury are not nearly so great as with lead, since the metal is much less widely used in the arts. On the other hand, it adheres more persistently to the skin, and is more readily absorbed and more toxic, so that a much smaller proportion of those exposed escape poisoning.

2. Actions in Acute Poisoning.[1]—**(a)** The *phenomena of the general poisoning by intravenous injection* consist in a very marked *fall of blood pressure,* due to a direct paralyzing action on both the **heart** and the **blood-vessels.** The former involves both ganglia and muscle. (v. Mering, 1880.)

(b) Mercury, however taken, has comparatively little effect on the **central nervous system,** especially in acute poisoning, the only symptoms which are noticed being secondary to the fall of blood pressure. *Consciousness* is usually preserved to the end. In chronic mercury-poisoning there is sometimes a noticeable tremor — *tremor mercurialis,* and a heightened psychic irritability — the so-called *erethismus.* These are probably of central origin. Sometimes, however, there is instead a *dulling* of the faculties. Mercury, like lead, may also produce *peripheral neuritis,* but much later than in the case of lead-poisoning.

(c) Local Action.— The general effects are largely overshadowed by the symptoms arising from the *local action,* which consists of a chemic irritation or corrosion:

1. These are most prominent in the alimentary canal, even when mercury has been given by any other channel — by inhalation or by hypodermic or intravenous injection. They may be due in part to the paralysis of the capillaries, but are mainly produced by direct chemic corrosion, since the metal is largely excreted through this channel. The result is a peculiar *gastro-enteritis.* It begins in the upper portion of the alimentary canal. There is an early *stomatitis* leading to ulceration, and this may extend so deep as to affect the bones, producing *necrosis of the jaw.* Increased *salivation* is a prominent symptom. It is probably due to the excretion of the mercury through the salivary glands. There is also a characteristic metallic taste. The gastro-enteritis is, however, most violent in the lower portions of the intestine, and the symptoms bear a

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[1] Exercise 32.

close resemblance to those of *dysentery*. The anatomic lesions — ulceration of cecum — are also similar.[1]

2. The excretion of mercury through the *skin* produces various *skin diseases;* the excretion through the kidneys, as has been said, nephritis. There is frequently a *formation of lime crystals* in the lumen of the tubules and possibly in the cells themselves. No explanation for this can be given. (Saikowsky, 1866.)

3. Course of Poisoning.— The *fatal dose* of mercuric chlorid is 0.18 Gm. Death may take place inside of half an hour, from collapse. More usually, however, the symptoms last several days; and death takes place from the lesions of the intestinal canal.

The acute poisoning may pass into the chronic form — *i. e.*, a single dose may be capable of producing chronic mercury-poisoning — since the mercury is excreted with such extreme slowness.

4. Treatment.— The *treatment of acute mercury-poisoning* will ordinarily be directed against the gastro-enteritis. The object will be to prevent the poison from coming in contact with the cells of the intestine, and also to convert it into a less irritant form. Since the corrosive and irritant action is due to its combining with nitrogenous material, it can be much lessened by the artificial introduction of such material.

The ordinary antidotes are *white of egg* and milk, which fulfill all these indications. The resulting compounds must of course be promptly removed by emetics or lavage, else they will be absorbed and produce general poisoning. One must be cautious not to introduce any common salt into the stomach as long as mercury is present; for this would increase the solubility of the latter.

III. CHRONIC MERCURY-POISONING.

(**a**) Chronic mercury-poisoning affects **metabolism** profoundly, producing cachexia. There are also *fatty degenerations* of the various organs, as in the case of arsenic or lead-poisoning. An occasional consequence of mercury-poisoning is *diabetes*. On the other hand, mercury is sometimes beneficial in diabetes if this is of syphilitic origin.

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[1] See plates 41, 42 and 43 of E. v. Hofmann, Atlas of Legal Medicine. W. B. Saunders, 1898.

The *chemic study* of these metabolic effects is very inconclusive and difficult, on account of the extensive action of mercury on the alimentary canal and upon the kidneys.

(b) It has been claimed that mercury produces a **rarefaction of bone.** This is undoubtedly found in a great many cases of chronic mercury-poisoning, but so far it has not been possible to exclude syphilis as the cause of the rarefying osteitis. It is quite conceivable, however, that mercury has such an action; for the amount of lactic acid in the blood is markedly increased by it, and this might effect solution of the lime salts, and this in turn might account for the calcareous deposits in the kidneys.

(c) It was formerly claimed that mercury possessed a marked *cholagogue* action. But it has been demonstrated on biliary fistulæ that the flow of bile is not increased.

The green color of the stools, on which this belief was based, is explained by the lessening of the putrefactive changes which are responsible for the conversion of the green bile pigments into those of the feces.

(d) Very small doses of mercury may have the same *beneficial effect upon metabolism* as small doses of arsenic, and probably act in much the same manner. The patient may increase in weight, and the number of red blood-corpuscles may rise, etc. (Schlesinger, 1884.)

(e) The **treatment of chronic mercury-poisoning** is the same as that of all chronic metal-poisoning, the object being to favor the elimination of the metal by all possible channels.

As has been said, it is claimed that potassium iodid hastens this elimination, and this has not been disproved. Hygiene is of great importance. For the stomatitis and salivation, cleanliness of the mouth and washing with alum or potassium chlorate are very efficient. The prophylaxis in factories where mercury is employed is the same as in the case of lead.

IV. THERAPEUTICS.

1. The use of mercury in **syphilis** rests entirely upon an empirical basis.

We do not even know whether its action is due to specific toxicity for the virus of syphilis or whether it is due simply to the general effects upon metabolism by actions analogous to those of arsenic. The former seems to be the case.

Although the usefulness of mercury in syphilitic disorders had up to recent years been a subject for much animated discussion, there appears to be at present no reason to doubt that it is *not only palliative, but curative, in the secondary stage of syphilis,* congenital as well as acquired; whilst it is useless in the first and third stages.

The first stage is best treated expectantly, the third with iodids. The other forms of treatment — sweating, diet, other metals (gold, etc.), sulphur-baths, and the various vegetable antisyphilitics — either act by supporting the mercury or are useless.

The mercurial treatment offers the greatest chances of success if it is *begun early* in the disease. In order to be of any permanent benefit it must be *continued for a considerable time* — several years — long after the symptoms have entirely disappeared. When used in this way there can be no doubt but that it frequently effects a *permanent cure*. The dose should never be kept at a point which would cause local symptoms.

2. The best method of **administration,** by the stomach, is to begin with small doses — perhaps one-third of the full dose — and increase these gradually — say 10% every day — until the first tenderness of the gums appears. The dose should then be cut down to half of that taken at this time and continued without further change.

The prolonged administration of mercury offers serious difficulties on account of its irritant action. Given by mouth it is very apt to produce gastro-enteritis, much more easily than when it is given by other channels. Since the irritation is due to its combination with the cell-proteids, this may be largely avoided by administering it in the form of proteid compounds — the albuminate or peptonate. The iodids possess some advantage over the chlorids in that they are more easily decomposed in the body. Whatever form is given, the patient should be placed upon an easily digested but nutritious diet. The state of the bowels should be carefully attended to.

If there is great urgency, or if the alimentary canal will not tolerate the mercury, it may also be introduced by other channels, but all have drawbacks.

The *intramuscular injection* of mercuric chlorid is extremely painful and may cause sloughing. The pain is less if sodium chlorid is added to the mercuric chlorid. It may also be diminished by using non-irritant combinations — the peptonate or albuminate dissolved by the aid of sodium carbonate or chlorid; or mercuric benzoate with sodium benzoate.

The cyanid may also be used hypodermically (0.003 to 0.005 Gm.). Suspensions of insoluble mercury preparations in oil appear useful for intra-gluteal injection, since the injections need only be made once or twice a week. Adeps Lanæ Hydrosus is the best menstruum, as it avoids the danger of embolism. The salicylate has been used in this way (0.1 Gm. in 2 c.c. of oil), as also a 50% emulsion of metallic mercury (one drop, gradually increased to 3 drops.)

For *inunction,* the mercury, usually in the form of a salve, is *rubbed into* the skin — *not* smeared over it. A piece of the ointment is rubbed into the surface of the skin until the mercury has disappeared. A new surface is taken each day, the round of the body being made in about six days. The *blue salve* is the most popular preparation. The officinal article may be improved upon by more thorough emulsification with soaps. The absorption of the ointment, as well as of the vapor in fumigation, can be rendered much more efficient by preceding it by a thorough diaphoresis. It is quite immaterial whether this be attained by teas, by hot baths, medicated or not, or by other means. For *fumigation* a gram of calomel is volatilized over an alcohol lamp in a closed chamber completely surrounding the patient, with the exception of the head. A rubber or other blanket answers the purpose very well. The *inhalation* is obsolete.

The *intravenous injection* of mercuric chlorid has also been successfully used, beginning with 6 to 8 mg. and increasing rapidly to 18 mg., repeating daily, and also giving mercury by mouth (Tommasali). Although no bad effects have been reported, the method is open to such grave dangers in inexperienced hands, that it will scarcely become popular.

3. Contraindications.— Mercury preparations are contraindicated whenever there is cachexia or any chronic disease in which the resistance of the body is lowered; for chronic poisoning is then induced very easily. Nor should it be employed when there is nephritis, nor after the sixth month of pregnancy, since mercury has a somewhat deleterious effect on the course of pregnancy and upon the child.

4. Of **other actions** the *diuresis,* caused by mild irritation from small doses, is used especially in heart disease (see page 684). The therapeutic uses resting upon its other local effects are discussed elsewhere. (Antiseptic, Chap. XVII; Parasiticide, Chap. XXIX, G; Intestinal, Chap. XXX, D and E.)

V. MATERIA MEDICA.

1. Preparations of Metallic Mercury:

Hydrargyrum (U.S.P., B.P.).—Hg. A fluid, silver-white metal. Sp. G. 13.535.

FOR INTERNAL USE.

	Average Dose. (U.S.P.).	Per Ct. of Hg.
Hydrargyrum cum Creta (U.S.P., B.P.).—(*Gray Powder*)	0.25 Gm. = 4 gr.	38.
Massa Hydrargyri (U.S.P.) } *Blue Mass..*	0.25 Gm. = 4 gr.	33.
Pilula Hydrargyri (B.P.) } *Blue Pill....*		

Colloidal Mercury (Hydrargyrum Colloidale, Hyrgolum) has recently been recommended as being less irritant and less toxic than ordinary mercury; it is at the same time more rapidly absorbed. The commercial product is still rather impure, and it has not received a sufficient trial to decide on its value. It is best employed by inunction (2 Gm. per day of a 10% ointment); but it may also be used by mouth (pills of 0.03 to 0.05 Gm.), and as a dusting powder for condylomata.

FOR EXTERNAL USE.

Unguentum Hydrargyri (U.S.P., B.P.).—*Mercurial Ointment.*—In suet and benzoinated lard .... (For inunction.)	....	50. % Hg.
Ung. Hydrarg. Dilutum (U.S.P.).—*Blue Ointment.*—⅔ of mercurial ointment, ⅓ petrolatum .... (For pediculi.)	....	33.5% Hg.
Ung. Hydrargyri Compositum (B.P.).—Contains camphor	....	...
Emplastrum Hydrargyri (U.S.P., B.P.)...	....	30. % Hg.

2. Mercurous Salts.—These are practically insoluble powders; not to be prescribed with iodids:

		Dose.
Hydrargyri Chloridum Mite (U.S.P.) *Hydrargyrum Subchloridum* (B.P.)	Hg.Cl. — *Mild Mercurous Chloride, Calomel* (white).	0.006 to 0.6 Gm. (1/10 to 10 grs.) U.S.P.: Laxative ......0.125 Gm. = 2 grs. Alterative .....0.065 Gm. = 1 gr.

Enters into:
- *Pil. Catharticæ Comp.* (U.S.P.)
- *Pil. Hydrarg. Subchlor. Comp.* (B.P.).
- *Ung. Hydrarg. Subchlor.* (B.P.).—10%.
- *Lotio Nigra* (B.P., N.F.) (*Black Wash*).—7.5 Gm. HgCl to liter of Lime-water Shake.

Hydrargyri Iodidum Flavum (U.S.P.). *Protoiodid of Mercury.*—HgI. Bright yellow. Generally administered as tablets .... 0.01 to 0.06 Gm. (⅙ to 1 gr.) (10 mg. = ⅕ gr., U.S.P.)

3. Mercuric Salts:

Hydrargyri Oxidum Rubrum
Hydrargyri Oxidum Flavum — (U.S.P., B.P.).—*Red and yellow mercuric oxid.*—HgO. Practically insol. powders. Not used internally. (The color depends on the method of preparation.

Ung. Hydrarg. Oxid. Rubri (U.S.P., B.P.)
Ung. Hydrarg. Oxid. Flavi (U.S.P.) — 10% in Wool Fat and White Petrolatum.

Ung. Hydrarg. Oxid. Flavi (B.P.).—2%.

Hydrargyri Chloridum Corrosium (U.S.P.)
Hydrargyrum Perchloridum (B.P.)
Mercuric Chlorid, Corrosive Sublimate — $HgCl_2$. Crystals or white powder. Sol. in 13 water, 3 alc.

Dose: 1 to 6 mg. (1/60 to 1/10 gr.) (3 mg. = 1/20 gr., U. S. P.).

Liquor Hydrarg. Perchlor. (B.P.).—1 ʒ = 1/16 gr. *Dose:* ½ to 1 ʒ.

Lotio Flava (B.P., N.F.).—3 parts $HgCl_2$ in 1,000 Lime-Water. Shake.

**Sal Alembroth.*—2 parts $HgCl_2$, 1 part NaCl. Less irritant.

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* Not official.

Hydrargyri Iodidum Rubrum (U.S.P., B.P.).— HgI_2. Red powder, almost insol. in water, freely sol. in solutions of iodids. *Dose:* As corrosive chlorid.

Liquor Arseni et Hydrargyri Iodidi.— See Index. *Dose:* 0.1 c. c. = 1½ ♏.

Hydrargyrum Ammoniatum (U.S.P., B.P.).— *White Precipitate.*— $HgNH_2Cl$ — 80% Hg. White powder, obtained by precipitating $HgCl_2$ with ammonia. Insol.

Ung. Hydrarg. Ammon. (U.S.P., B.P.).— 10% in Wool-Fat and White Petrolatum.

Oleatum Hydrargyri (U.S.P.).— 25% of yellow mercuric oxid.

Ung. Hydrarg. Oleat. (B.P.).— 1 in 4.

Liquor Hydrargyri Nitratis (U.S.P., B.P.).— 60% $Hg(NO_3)_2$ and 11% HNO_3. Caustic.

Ung. Hydrarg. Nitratis (U.S.P., B.P.).— *Citrine Ointment.*— 7% of mercury, dissolved in nitric acid, and suspended in lard. Used on ulcers. Irritant.

* *Hydrargyri Cyanidum.*— $Hg(CN)_2$.—Sol. in 13 water. White powder: 1 to 6 mg. = $^1/_{60}$ to $^1/_{10}$ gr.

* *Hydrargyri Subsulphas Flavus.*— $Hg(HgO)_2SO_4$.— *Turpeth Mineral.*— Yellow powder.

XVII. LEAD.

The phenomena of lead-poisoning are characterized by the ***independent involvment of very numerous and diverse organs.*** Lead, in this respect, occupies a rather peculiar position amongst the metals, and, indeed, amongst all poisons. For whilst so extensive an action suggests the idea of a general toxicity to protoplasm, this does not seem to exist, since lead is comparatively non-toxic to lower organisms. It is a specialized poison; but it is specialized for quite a number of tissues and organs.

I. ABSORPTION, ETC.— ETIOLOGY OF POISONING.

The action of lead is influenced so greatly by its absorption, retention, and excretion that it will be well to discuss these subjects first.

Lead salts are astringent rather than corrosive. They may cause sufficient corrosion to be absorbed, but this absorption is never sufficient to cause *acute* fatal poisoning from systemic effects. At least, no case is on record in which this has occurred. A very small amount, however, is absorbed fairly readily, in whatever form the lead is given and whether in large or small doses. This is quite insufficient to cause any immediate symptoms. But these traces are excreted extremely slowly, and this ready absorption and slow excretion furnish the conditions for cumulative action.

In this way it is responsible for very many deaths, many more than arsenic. Lead may be absorbed from any part of the surface of the body — from the skin as well as from the alimentary canal. *Hair dyes* containing lead are a frequent source of poisoning; but the absorption is much greater from the mucous membranes, and the gastro-intestinal tract forms by far the most common way of entrance.

Occasions for the introduction of lead are very numerous. The metal is used extensively in the *arts*, and the workers in these—painters, dyers, type-setters and type-founders, plumbers, etc.—are the most frequent sufferers after lead miners and the working-men in white-lead factories. Artisans working with lead-paints are by far the most common victims.[1]

But the occurrence of chronic lead-poisoning is by no means confined to these artisans. The metal is so widely distributed that every one is to some extent exposed. Some of the ways in which poisoning has occurred are very surprising. Others are more easily understood. Perhaps the first of these to come to the mind is the *lead of water-pipes*. The opinion amongst medico-legal authorities as to the danger of lead-pipe has varied considerably. But at the present time it seems to be accepted that, if perfectly pure water is allowed to flow through bright and clean lead-pipes, poisoning results invariably. In this case the surface of the lead is changed into a hydrate (Clowes, 1902), and this is sufficiently soluble to cause the intoxication. But the danger is very much less with old lead-pipes as ordinarily used; these have become lined with a layer of lead oxid, PbO + Pb. This is quite insoluble, and does not form a hydrate. The chance of solution is still less if the water contains calcium carbonate and carbonic acid. Ordinarily lead-pipes would therefore present but little danger. But even then, if the water is allowed to stand a long time in the pipes, some solution is bound to occur. On account of this danger, lead-pipes should be condemned.

The employment of lead *vessels for cooking* should, of course, be entirely discarded. *Tinned vessels*, especially tin cans, usually also contain a certain amount of lead in the solder. If the percentage does not exceed a certain limit, the lead seems so firmly combined in the alloy as to prevent its solution even by moderately acid liquids, such as vinegar. If it exceeds this quantity, a certain amount will be dissolved, and will exert its toxic action.[2] The addition of some lead is also necessary in tin-foil, such as is used for wrapping articles of food, to make the tin workable. Here, also, it is harmless if it does not exceed a certain limit. Lead enters into the glazing of *earthenware* vessels, and is contained in many varieties of *glass*; but if it exists entirely in the form of silicate of lead, it presents no danger. All these vessels may be easily tested with sufficient accuracy by allowing vinegar or dilute acetic acid to stand in them for twenty-four hours and then passing a current of sulphuretted hydrogen through the liquid. If there is no precipitate, the amount of lead is below the dangerous limit. It is a somewhat peculiar fact that lead bullets in a wound do not seem to exert the lead action. They probably become oxidized in such a way that none of the metal is absorbed.

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[1] The smoke and fumes from lead factories contain quite a large amount of the metal. This is deposited on the soil and on the surface of plants, and is also taken up into the tissues of the latter. Cases of poisoning have been referred to the milk of cows fed on these.

[2] In Germany, Austria, and some other countries, the lead in solder which comes in contact with food is limited by law to 10%, in tin plate to 1%, and in France only half of this amount is permitted. None of the States in the Union place any limit on this, desirable as it appears from a hygienic standpoint.

The lead is always absorbed in the form of *soluble proteid combinations*. These may be formed from lead compounds which are perfectly insoluble in water or acids. Even *lead sulphate*, one of the most insoluble of substances, will be absorbed in sufficient amount to produce poisoning, so that sulphuric acid is useless as a prophylactic.

Excretion.— Lead is excreted by all channels, possibly with the exception of the sweat. The principal path is by the epithelium of the skin and especially of the alimentary canal. It is said that chronic lead-poisoning may usually be detected by painting the skin with sulphid of ammonium, this giving a black color. In painters this is perhaps often due to the adherence of lead to the skin.

A part of the lead is excreted by the urine, where it may be detected for forty days after the administration. The excretion is at first hastened by potassium iodid (Melsens, 1849); but this soon ceases to be effective.

The lead is also commonly deposited in the shape of sulphid on the edge of the gums, giving the characteristic "*lead line*." The *feces* in lead-poisoning also very frequently have a dark color from the action of the H_2S formed in the intestines, upon the excreted lead.

Retention.— The lead which is retained in the body is stored especially in the liver and other organs, the blood containing only very small traces.[1]

There is a very great individual variability in the **susceptibility** to lead-poisoning; with a number of persons exposed to the same conditions, and using the same precautions, some will be violently poisoned and others not at all. This depends perhaps upon differences in absorption and excretion, but anemic patients and persons with low resistance generally are very susceptible.

II. PHENOMENA OF LEAD-POISONING.

The primary symptoms of chronic lead-poisoning consist in local irritation, changes of metabolism, and in nervous phenomena, mainly of central origin.

The systemic actions do not occur in any regular order, so that evidently they do not depend one upon another.

1. The **local irritant action** is seen mainly in acute poisoning.

(**a**) **Alimentary Canal.**— Lead acetate and most lead preparations have a sweetish astringent *taste*. This is soon followed by the usual *symptoms of irritation in the alimen-*

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[1] Liver	0.03	to	1.00 %
Kidney	0.03	"	0.07 %
Brain	0.02	"	0.05 %
Bones	0.01	"	0.04 %
Muscles	0.004	"	0.008%
Blood	traces.		

tary canal: salivation, dysphagia, vomiting, and diarrhea, etc. The vomit is sometimes bloody. The diarrhea is not as profuse in lead-poisoning as it is with most irritant poisons, on account of the astringent action.

The lead salts, like some other metallic salts, form an insoluble coating over the mucous membrane of the intestine, and so prevent the ordinary lead preparations from penetrating and from causing deep corrosion and extensive absorption.

(b) Another evidence of the irritant action of lead is found at the point of excretion; that is to say, in the **kidneys.** Nephritis is a very common consequence of acute lead-poisoning, and an invariable accompaniment of chronic intoxication. In the latter case it may be in part secondary to some of the other effects of the lead: viz., the gout or the arteriosclerosis.

(c) The local irritant actions upon the alimentary canal and upon the kidneys help to explain the **metabolic changes,** but these are also in part direct, in part secondary to the vascular injury. The chemic changes are rather obscure. There is a profound *anemia.* The pallor is at first due merely to constriction of the cutaneous vessels; but later there is a diminution of hemoglobin and of the number of red corpuscles. The latter undergo a granular degeneration. Their destruction very frequently gives rise to *icterus.* The *intima of the blood-vessels* undergoes fatty degeneration, and this is frequently followed by *arteriosclerosis. Fatty degenerations* are also found in other organs: in the kidneys, liver, and other glands. Another expression of the perverted metabolism is the occasional production of *gout.*

Lead always exerts an unfavorable influence upon *pregnancy.* The number of miscarriages in women affected by lead-poisoning is very large; and of the children born, by far the largest proportion die during the first year of life.

2. The effects of lead-poisoning upon the **peripheral nerves** and muscles are very often characterized by the fact that the symptoms appear suddenly, last for quite a short time,— several hours, perhaps,— and then disappear, to recur later.

(a) The most conspicuous of these peripheral effects is **lead colic.**[1]

It is characterized by violent pains, localized especially near the umbilicus. The abdomen is very conspicuously contracted, even scaphoid. The patient frequently lies on his face, with the fists pressed against the painful region, since pressure relieves the distress.

This colic is caused by the violent contraction of the intestinal muscles. Since this forces the blood out of the vessels of the splanchnic area, the general blood pressure will rise, the pulse will be hard and tense, and the heart will be slowed.

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[1] **This is produced as readily by the hypodermic or intravenous administration of lead, as when it is taken by mouth.**

The cause of this contraction must be a *stimulation of the nerve endings,* since it does not possess the peristaltic character of the ganglionic stimulation and is entirely abolished by atropin. It is largely relieved by measures which dilate the blood-vessels, for instance, nitrites, so that one is justified in assuming a primary vasoconstriction as one of its causes.

(b) **Of other affections of the peripheral nerves,** *anesthesia* or disturbed sensation of the skin, and more rarely of underlying organs, is conspicuous.

A striking instance of this disturbed sensation is the *arthralgia saturnina,* a painful affection of the joints and adjacent muscles. The pain is very violent, as in the colic, which it resembles closely. Like this, it appears suddenly, lasts a few hours, disappears, and recurs.[1]

Neuralgias occur occasionally. They have perhaps several explanations: In some cases they are due to a peripheral neuritis, in others to an action on the central nervous system.

(c) The actions on the **motor system** consist in neuritis, paralysis, and atrophy.

The seat of this action has given rise to considerable discussion. It has been placed in the central nervous system, in the peripheral nerves, and in the muscle cells. The last two are probably the usual seat, but the central nervous system may undoubtedly participate in some cases.

The action of lead upon *isolated muscle* is quite characteristic. There is at first an increase in the ease with which the muscle is fatigued, and the fatigue curve presents some very peculiar changes. In the normal fatigue curve the height of the successive contractions decreases in a perfectly regular manner; if a line is drawn joining the summits of contractions, this is practically straight. But if fatigue is produced in a muscle poisoned by lead, the line is extremely irregular. One contraction will be very low, another high, etc. It will also require a less number of contractions to produce complete fatigue than in the case of normal muscle (Harnack, 1878).

In chronic poisoning in the intact animal *early fatigue* is also a prominent symptom. This gives way to *paralysis.* The paralysis is followed by total *atrophy*.

The onset is slow. The muscles first become insensitive to voluntary stimulation and later to electric. At this time the reaction of degeneration sets in; that is to say, the muscle is hypersensitive to galvanic, and less sensitive than normal to faradic stimulation.

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[1] This arthralgia is not seen in animals; but these seem to be much less sensitive to articular pain than man. They also show very little distress if acute arthritis is produced by uric acid injection.

The **heart** may be similarly affected, and this quite early in the poisoning; this is the case especially if the poison is injected directly into the blood.

The action upon the *peripheral motor nerves* is probably quite similar to the direct muscular action.

This paralysis of the extensor muscles has been advanced to explain a very common phenomenon of lead-poisoning, the **drop wrist** or lead wrist. Others, however, attempt to explain it by active contracture of the opposing flexor muscles. It is not unlikely that both have a part in the explanation.

The contracture begins at the metacarpo-carpal articulation of the two middle fingers, then the two outer fingers and the thumb, and then the wrist.

3. The effects upon the **central nervous system** constitute what is called *encephalopathia saturnalis*. They are exerted especially on the cortex. There is first irritation, which is followed by paralysis. The effects are both sensory and *motor*, but particularly the latter. They begin with contractures, then choreic movements, then possibly generalized *convulsions*.[1]

Later the motor stimulation gives place to paralysis.

On the part of the *mental and psychic faculties* there is delirium, then depression, and in the last stages, coma. The latter may also be uremic. Lead-poisoning is claimed as a contributory factor of insanity.

It is said that in very prolonged cases of lead-poisoning, the anterior columns of the spinal cord show histologic degenerations. A case of criminal poisoning is known where small doses were administered during six months. The symptoms were described as persistent vomiting, constipation, and colic, followed by paresis and epileptiform convulsions. Symptoms similar in all respects to the above may be evoked in animals by the injection of organic lead preparations such as lead-triethyl (Harnack, 1878).[2]

III. TREATMENT OF LEAD-POISONING.

In acute lead-poisoning it is well to administer a sulphate, so as to render the lead as far as possible insoluble, and then to remove it quickly by means of an emetic.

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[1] The convulsions which are seen in lead-poisoning are not always due to the lead itself, but sometimes to the nephritis; *i. e.*, uremic.

[2] The metal **Thallium** resembles Lead in its action. The acetate has been used in doses of 0.005 to 0.01 Gm. per day, against the night-sweats of phthisis. It caused neuritis, and its use is not justified.

In chronic lead-poisoning removal of the lead is also one of the main indications. Hot baths are efficient for this purpose, as also the administration of potassium iodid in fairly large doses. For the rest, the treatment must be purely symptomatic: For the colic, belladonna, opium, and the nitrites; for the prevention of paralysis and atrophy, strychnin, massage, electricity, etc.

Prophylaxis is of the greatest importance. The public should be thoroughly educated to the insidious dangers of lead, and the chances of poisoning carefully guarded against. The sources of danger — lead-pipes, etc.— should be eliminated. Tin cans, foil, etc., should be frequently examined by authorized persons. Special precautions are required in lead factories and in exposed trades. Since the main channel of poisoning is by the mouth, extreme cleanliness should be encouraged and made possible by liberal facilities for washing. Food should not be permitted on the premises, and the clothing should be changed before leaving the works. More stringent laws are greatly needed in this connection.

IV. THERAPEUTICS.

The therapeutic importance of lead rests entirely upon its local astringent actions. The local application of an alcoholic solution of lead acetate constitute the best treatment of *ivy-poisoning*. It may be doubted whether the use of lead for any other therapeutic purpose is justifiable, in view of its dangers. It should never be taken internally, and should never be continued for a long time.

V. MATERIA MEDICA.

Plumbi Acetas (U. S. P., B. P.).—*Sugar of Lead.*— $Pb(C_2H_3O)_2 + 3H_2O$. White crystals. Sol. in 2 water, 30 alcohol. *Dose:* 0.065 Gm. = 1 gr. (U. S. P.). Externally, sat. alc. sol. for ivy-poisoning.

Ung. Plumb. Acet. (B. P.).— 4%.

Suppos. Plumb. Comp. (B. P.).— 3 grs. lead acetate and 1 gr. opium.

Pil. Plumbi cum Opio (B. P.).— 12½% opium. *Dose:* 2 to 4 grs.

Liquor Plumbi Subacetatis (U. S. P.) [——— *fortis,* B. P.].—*Goulard's Extract.*— 25% $Pb_2O(C_2H_3O_2)_2$.— Used only for making preparations.

Ceratum Plumbi Subacetatis (U. S. P.).— 20% of the solution.

Liquor Plump. Subacet. Dilutus (U. S. P., B. P.).—*Lead Water,* — 4% of solution = 1% of salt. Externally.

Glycerinum Plumb. Subacet. (B. P.).

Plumbi Iodidum (U. S. P., B. P.).— PbI_2.— Bright yellow powder, almost insol.

Emplastr. and *Ung. Plumbi Iodidi* (B. P.).

Plumbi Nitras (U. S. P.).— $Pb(NO_3)_2$.— Colorless crystals, sol. in 1.85 water, almost insol. in alcohol.
Plumbi Oxidum (U. S. P., B. P.).— *Litharge.* PbO. Reddish yellow powder, almost insol.
Plumbi Carbonas (B. P.).— *White Lead.*— $(PbCO_3)_2Pb(OH)_2$. Insol.
Ung. Plumbi Carbon. (B. P.).
Emplastrum Plumbi (U. S. P., B. P.).— *Diachylon* or *Lead Plaster.*— A lead-soap, made by precipitating soap with lead acetate.

Study Materia Medica Lesson 51.

XVIII. PHOSPHORUS.

I. VARIETIES.

The element phosphorus exists in two forms, the red and yellow. The former is non-volatile, and is insoluble in water or oil, is not absorbed, and is therefore not toxic. The yellow or ordinary phosphorus, whilst also insoluble in water, is very volatile, and penetrates the tissues with ease, especially when in finely divided state, or when dissolved in fats. Phosphorus acts as such, the compounds being harmless and having a totally different action.

II. SUMMARY OF ACTIONS.

1. Direct paralysis of cardiac muscle.
2. Changes in metabolism, consisting in an increased decomposition of proteids; diminished oxidation; fatty infiltration of epithelium and muscle, with subsequent connective-tissue infiltration; increased formation of sarcolactic acid; modifications in bone-formation and in the blood.

III. DETAILS OF ACTION.

1. The one acute and direct action of phosphorus is on the **heart.** Large doses paralyze this organ, acting apparently on the muscle-fibers. (Phosphorus has no action on muscle-nerve preparations.) There is consequently a fall of blood-pressure and eventually cessation of cardiac action. (Meyer, 1881).

Action on Metabolism.— This is the most interesting feature of phosphorus-poisoning from a scientific standpoint, being almost unique. It occurs in chronic poisoning, or as a secondary process after a single larger dose.

It cannot be said that the process is very thoroughly understood. It may be reduced to an increased metabolism of nitrogen, and a diminished oxidation. But what relation these two processes bear to each other cannot be stated.

(A) Nitrogen Metabolism.— This is very greatly increased, as much as 300% (Storch, 1865). All the nitrogenous metabolites participate in this increase (v. Jaksch, 1903); but not to the same extent (Münzer, 1894). The urea is not nearly so much increased as the others, and may even be less than normal. It is to a large extent replaced by ammonia. This may be attributed to an increased production of sarcolactic acid. But, in addition, some of the N is excreted in the urine in less completely oxidized form, as leucin, tyrosin, and peptone-like bodies (Schultzen and Ries, 1869).

Some light is thrown on the metabolic action of phosphorus by the observation of Jacoby, that it greatly increases the autolysis of the liver, by lessening the resistance to the normal autolytic ferments. Fibrinogen is very easily autolyzed, so that it disappears in phosphorus poisoning, the blood thereby becoming noncoagulable.

(B) A rise in the metabolism of cell-proteids always causes **fatty changes** of cells. (This is also seen with phlorrhizin, arsenic, antimony, many volatile oils, alcohol group, benzol, phallin, etc.) In the case of phosphorus, the main effect falls upon the liver cells, but practically all other cellular organs are involved: muscle, skeletal, and cardiac; kidneys; blood-vessels; epithelium of stomach and intestine, etc. The fatty changes are preceded by "cloudy swelling," which is probably an intermediate stage. They are followed by proliferation of interstitial connective tissue (cirrhosis).

The question is still under discussion as to whether the fatty changes are infiltrations or degenerations; whether the fat is merely transported from other portions of the body, or formed *in situ*. The bulk of the evidence is in favor of infiltration. There seems to be no doubt that the total amount of body-fat in the frog is not increased; and it is stated that the fat in the phosphorus-liver does not differ in composition from the body-fat. Since the proteids are diminished, as also the glycogen, the hypothesis is not improbable that the fatty changes in this, as in other conditions, are the expression of starvation. The cell, on being deprived of its ordinary food, draws on the fat of adipose structures to supply the deficiency.

(*a*) The changes in the *Liver* consist, then, in increase of fat (three to four times the normal amount); diminution of glycogen; increased formation of ammonia, and of leucin and tyrosin.

There are also marked changes in the *bile*. At first there is an increased formation and excretion of bile pigment. This is perhaps in part due to a destruction of red blood-cells, in part to an increased activity of the hepatic epithelium. Later the bile-pigments are retained, leading to *icterus*; whilst a thin fluid is excreted, which is probably mainly mucus. The suppression of the bile secretion is presumably due to occlusion of the bile capillaries; at first, through the fatty enlargement; later, through the cirrhosis.

(*b*) The degeneration of the *muscles* leads to debility; of the *heart*, to weakening of the circulation; of the *kidneys*, to albuminuria, which is never very severe.

(*c*) Degeneration of the *blood-vessels* leads to loss of elasticity and to capillary hemorrhages. It may also be in part responsible for some of the other changes. The *blood* shows several changes: Its osmotic pressure rises (to Δ 0.612; Bottazzi, 1896). It is rendered noncoagulable (probably by destruction of the fibrin ferment; due perhaps to the production of peptone in the autolysis of the organs (Cevidalli, 1902). The red corpuscles are destroyed. This does not lead to hemoglobinemia, the iron being deposited in the liver, spleen, marrow and lymph glands, and excreted by the bile (Vogel, 1902). The sugar of the blood is increased (Heinsberg, 1895).

(*d*) The degeneration of the *cells of the gastric and intestinal mucosa* explains the abdominal pain, vomiting, and occasional diarrhea. These occur equally readily after hypodermic injection, so that they are not due to a local action, but rest on the metabolic changes.

(C) **Other Effects.**— The use of *O* and the excretion of CO_2 are diminished.

The P_2O_5 *in the urine is increased*, but much beyond the amount of P administered. This is only another expression of the increased proteid metabolism. The NaCl is diminished on account of the anorexia.

The *growth of young bones* is affected in a peculiar manner, somewhat as with arsenic, the cancellous tissue tending to become compact (Wegner, 1872). This bone is of normal structure and composition. Phosphorus also stimulates callus-formation.

Small and often repeated doses of phosphorus are sometimes used by the laity to procure *abortion*. It acts indirectly through the changes in circulation and nutrition, and is dangerous.

The *central nervous system* is not affected directly.

Phosphoretted Hydrogen causes a very similar intoxication.

IV. TOXICOLOGY.

1. **Etiology.**— Phosphorus is quite accessible in the form of matches or phosphorus rat paste, so that poisoning, accidental or suicidal, is not at all rare. Chronic poisoning of a somewhat different character is seen from its fumes, in phosphorus and match factories. This, as well as the poisoning by matches, has been very greatly diminished since the introduction of amorphous (red) phosphorus.[1].

Phosphorus burns are no more dangerous than other burns of similar extent and do not exhibit any of the symptoms of phosphorus-poisoning.

2. The **symptoms** appear usually only after some hours, and begin with burning and pain in the abdomen, and vomiting. The vomit has the odor of garlic, and is luminous in the dark. The patient then usually improves greatly, and appears normal for two or three days. At the end of this time, icterus makes its appearance, together with abdominal pain and tenderness; emesis, often bloody; and diarrhea. The area of liver-dullness is increased. There is considerable muscular weakness and pain, and general prostration; the pulse is small and quick. The urine contains bile, albumin, leucin, tyrosin, an abnormal amount of ammonia, etc., sometimes blood. Hemorrhages occur in many different situations. There is usually a fever, but sometimes abnormally low temperature. This condition lasts five to eight days, when the patient usually dies of heart failure. Recovery is possible, however, even when the symptoms are very severe.

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[1] The first phosphorus friction matches were made by Dérosne, Paris, in 1816, but they did not become practical until 1833, when processes for their manufacture were invented in several countries. These all employed yellow phosporus; each match contains 3 to 5 mg., so that 16 would be fatal for an adult.

The more modern amorphous phosphorus matches contain, besides this, some oxidizing agent ($KClO_3$, KNO_3, chromatic or oxid of Mn, Pb, Fe) and paraffin, glue, etc.

The "safety matches" have no phosphorus on the sticks, which are usually headed with Sb_2SO_3, $KClO_3$ and glue; the phosphorus is here on the friction surface coating the box.

Phosphorus-poisoning may be recognized by the odor, by the chemic examination of the urine, and the fatty changes in organs.[1]

The *fatal dose* is 50 mg.; but 13 mg. cause very grave intoxication.

3. The treatment consists, in the early stages, in the administration of $CuSO_4$ as emetic: the Cu is precipitated in metallic form on the P globules and retards their absorption. The stomach should then be washed with 0.2% $KMnO_4$ or with H_2O_2. Old spirits of turpentine in doses of 1 to 2 c.c. should be given several times a day for some days. All these measures are for the purpose of oxidizing the phosphorus. Oils and fats of all kinds must be avoided. Alkalies are useful to neutralize the excessive sarcolactic acid. For the rest, the treatment must be symptomatic.

A peculiar *necrosis of the jaws*, as observed in match factories, begins with salivation, suppurative ulceration of the gums, and ends in a very profound periostitis, involving the whole jaw. It usually starts in carious teeth. The lower jaw is more often affected. The only treatment is excision of the diseased bone. The lesions are referred by some authors to the phosphorus itself; by others, to the lower oxidation compounds.

Phossy Jaw.

V. THERAPEUTICS.

The only rational indication for phosphorus is in deficient lime deposition in bone, as in rickets, osteomalacia, and ununited fracture. However, the evidence in regard to its benefits is not very conclusive, and it is certainly a very dangerous remedy. The first effects are to be seen in about four weeks. It must be omitted if gastric symptoms appear.

Its use in diseases of the nervous system — alcoholism, sexual exhaustion, neuralgia, etc.— is not supported by any pharmacologic action, nor by clinical results; nor has its use in chlorosis any scientific basis.

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[1] See E. v. Hofmann, plate 48.

VI. MATERIA MEDICA.

Phosphorus (U. S. P., B. P.).— The waxy variety. Nearly insol. in water; sol. in 350 absolute alc., in 50 fatty oil; in ether or chloroform. Very sol. in carbon disulphid. *Dose:* 0.5 to 3 mg. = $^1/_{100}$ to $^1/_{20}$ gr. (0.5 mg. = $^1/_{128}$ gr. U. S. P.).

Pilulæ Phosphori (U. S. P.).— 0.6 mg. = $^1/_{128}$ gr.; coated with Tolu to prevent oxidation.

Pilula Phosphori (B. P.).— 2%. *Dose:* 1 gr.

Oleum Phosphoratum (B. P.).— 1%. *Dose:* 1 to 5♏, B. P. This and the *Spiritus Phosphori* (0.12%, *dose:* 0.3 to 1 c. c. = 5 to 15 ♏) have been discarded from the U. S. P., on account of their very uncertain strength; they deteriorate rapidly. It is better to prescribe an extemporaneous solution in almond or cod-liver oil.

VII. HYPOPHOSPHITES, GLYCERINO-PHOSPHATES, AND LECITHIN.

Phosphorus occurs in many animal and vegetable cells, as *lecithin* (esters of the fatty acids with glycerino-phosphoric acid and cholin), combined with proteids as vitellin, etc. The large quantity of this element in nervous tissues has led to persistent attempts to use phosphorus and its salts as "*nerve foods,*" or tonics in neurasthenia, cachexia, scrofula, neuritis, incipient phthisis, etc. *Phosphorus, phosphates, hypophosphites,* and more recently *glycerino-phosphates* have been tried for this purpose. Metabolism experiments have been uniformly negative, and the clinical results are so indefinite and contradictory that these compounds must be adjudged devoid of any action. There is no evidence that inorganic phosphorus compounds are ever transformed into lecithin. They are all excreted as phosphates.

The latest steps in this direction is the introduction of **lecithin.** This is no longer advanced as a nerve-food, but as a general nutritive tonic. It is claimed that it increases the weight and rate of growth in young animals (also in plants). It acts as a stimulant to nutrition, and not as a direct nutrient (the effective dose being too small for the latter explanation). The proportion of red blood corpuscles is increased, and the hemoglobin rises in the same ratio. There is also a slight increase of mononuclear leucocytes.

The appetite and the utilization of nitrogen are improved. The urine shows characteristic changes: the daily quantity, the phosphates and sulphates are not altered, but the excretion of total nitrogen and urea is very markedly increased; the acidity is somewhat heightened; the uric acide is perhaps slightly diminished.

These urinary changes persist for about five months under the continuous administration of lecithin, when they return to normal. This habituation also applies to the effect on nutrition, the drug becoming inactive after a time.

The actions may be produced both by oral and by hypodermic administration. It has been suggested that large doses might become dangerous through the liberation of the toxic cholin; but this does not seem to occur, for very large doses are not toxic. It is useless, however, to increase or continue the drug if the ordinary doses do not cause noticeable improvement within ten days.

These reports refer to the isolated lecithin. Since this is a rather expensive article, it would seem preferable to secure them by the use of egg-yolk, which contains about 68% of lecithin. It has been pointed out, however, that the ordinary diet contains from 5 to 8 grams of lecithin, *i. e.*, much more than the effective therapeutic quantity; and it is therefor assumed by some authors that the combined lecithin for some reason lacks the peculiar qualities of the freed lecithin. The question is not settled.

Therapeutics: Lecithin is not specific in any disease, but is advised whenever there is faulty nutrition or growth; in artificially fed infants, anemia, chlorosis, debility, convalescence, tuberculosis, tabes, neurasthenia, diabetes (especially pancreatic), rachitis, senility, cachexia,, etc.

MATERIA MEDICA.

Hypophosphites:

The dose of the dry salts is 0.12 to 1.2 Gm. (2 to 20 grains). They are soluble in 1 to 8 parts of water.

Calcii Hypophosphis.— $(CaPH_2O_2)_2$ (U. S. P., B. P.).

Sodii Hypophosphis.— $NaPH_2O_2 + H_2O$ (U. S. P., B. P.).

Potassii Hypophosphis.— KPH_2O_2 (U. S. P.).

Ferri Hypophosphis.— $Fe_2(PH_2O_2)_6$ (U. S. P.). Insoluble.

Mangani Hypophosphis.— $Mn(PH_2O_2)_2$ (U. S. P.).

Acidum Hypophosphorosum (U. S. P.).—30% $H.PO_2H_2$.

Acidum Hypophosphorosum Dilutum (U. S. P.).— 10%. *Dose:* 0.5 c. c. = 8 ♏.

Syrupus Hypophosphitum (U. S. P.).— Contains the hypophosphites of Ca, K, and Na, with dilute hypophosphorous acid, flavored with lemon. *Dose:* 8 c. c. = 2ʒ (U. S. P.).

Syrupus Hypophosphitum cum Ferro (U. S. P.).— Contains the above, also the hypophosphites of Fe and Mn, with quinin and strychnin. *Dose:* 8 c. c. = 2ʒ (U. S. P.) = 9 mg. (1/7 gr.) quinin; 0.9 mg. (1/70 gr.) strychnin.

Glycerino-Phosphates:

The glycerino-phosphates of the alkalies and earths, as also of iron, are all soluble, the first even hygroscopic. The calcium salt, which is soluble in 20 parts of water, has been particularly recommended. The *dose* is 0.1 to 0.4 Gm. The sodium salt, which is furnished in 75% solution, is better adapted to hypodermic use. The solutions should not be heated.

Glycerino-phosphoric acid has the formula $O = PH(OH)(OC_3H.OH)$.

Lecithin: Occurs as a yellowish-brown, waxy solid, of peculiar odor, insoluble in water, soluble in absolute alcohol and fat-solvents. It contains 3.84 to 4.12% of phosphorus. Incompatible with alkalies. *Dose,* by mouth, 0.1 to 0.5 Gm. (1½ to 8 grains) per day, as pills, before meals; hypodermically 1 c. c. of 5% solution in oil, daily. The oral administration is preferred. Infants, one-third of these doses.

Study Materia Medica Lesson 51

PART II. SECTION B.

LOCALLY ACTING DRUGS.

CHAPTER XXVIII.

IRRITANTS, CORROSIVES AND ASTRINGENTS.

(INORGANIC IRRITANTS AND TANNINS).

(A) GENERAL CONSIDERATION OF IRRITANT ACTION.

The local actions of drugs are, as a rule, simple and uniform, since they can occur ordinarily in only a few situations, especially the skin and mucous membranes. These agree closely in structure and functions. There are therefore many phenomena which hold true of all local irritant poisons. These may be studied once for all, and present only minor modifications in individual cases.

The majority of local poisons produce the typical phenomena of inflammation ("irritation"), by causing necrosis of protoplasm through coagulation, liquefaction, etc. Most of these reactions are purely chemic or physical, and can be reproduced in the test-tube with proteids.[1] Remembering the extreme sensitiveness of protoplasm to reagents, it will be readily understood that almost all substances — even water — may be irritant under suitable conditions.

1. PHENOMENA OF IRRITATION.

1. These can be studied very typically on the **skin.**[2] The first degree of irritant action is shown in an arterial and capillary hyperemia, at first active, later passive. This constitutes the "dermatitis erythematosa" of the dermatologists. Or, speaking pharmacologically, it constitutes **rubefaction,** and the agents which produce it are therefore called rubefacients. The congestion is accompanied by sensory stimulation — by itching or pain.

If the irritant action does not go any further than this, resolution takes place without leaving any lesions, simply by a return of the vessels to normal. Usually the upper layers of the skin are desquamated.

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[1] Exercises 15, 16 and 17.

[2] Exercise 18.

If the action is stronger than rubefaction, it may pass into vesication or pustulation. **Vesication** occurs if the inflammatory action results in the formation of an exudate greater in amount than can be carried off by the lymphatics. Every hyperemia is, of course, accompanied by an increase of exudation, but up to a certain amount, as in rubefaction, this is readily reabsorbed. When this limit is exceeded, an actual, visible, effusion results. This liquid will accumulate in the parts of the tissues offering the least resistance to distention. In the case of the skin, it penetrates readily through the lower layers of the rete Malpighii, but is arrested by the impermeable stratum corneum. It is therefore confined between the upper and lower layers of the rete Malpighii, and separates them, in this way causing blisters or vesicles. The agents which produce these are called *vesicants* or *epispastics*.

Resolution takes place in these cases without loss of tissue, by the formation of a new stratum corneum from the remaining rete Malpighii.

If the overlying and separated layers of epidermis are removed, there is much chance of infection, the lower layers of the rete Malpighii offering but little resistance. In this way there may be a loss of substance from secondary infection. The sensory stimulation of this vesication is still stronger than that of rubefaction.

If the inflammation, instead of leading to an effusion of liquid, leads to an emigration of leucocytes, it produces **pustulation,** the agent being called a *pustulant*. This depends to some degree upon the violence of the inflammation, a more profound irritation being required to produce an emigration of leucocytes than what suffices to cause an effusion. But to some extent it is also a specific property of the pustulant. Certain vesicants never produce pustulation, whilst certain pustulants do not vesicate. The pustulant action is probably the more common when there is a special involvement of the cutaneous glands. Indeed, it is usually confined to these, and is but rarely diffuse, for the reason that both the irritant and the bacteria can penetrate more readily at these points. In other cases, as with tartar emetic and the bromids, the acid secretion of these glands dissolves or liberates the irritant agent.

Aseptic Pus Formation.— A few drugs possess a specific chemotactic power on leucytes; so that their injection (hypodermic or into serous cavities) leads to the collection of pus, even when asepsis is perfect. Turpentine, croton oil, petroleum, mercury, silver nitrate, digitoxin, cadaverin, aleuron suspensions, etc., are the principal examples.

In pustulation there is necessarily always some loss of tissue and scar formation. Sensory stimulation is still stronger than in the case of the vesicants.

If the inflammation exceeds this degree, it leads to necrosis of the cells; and **corrosion**, or *cauterization,* results. This is the last degree of the inflammatory action. Destruction of tissue by irritants may be the result either of inflammatory necrosis or of a direct chemic action.

The stronger acids and alkalies, as also bromins and some of the metallic poisons, such as arsenic and mercury, form soluble compounds with proteids, and produce solution in this manner. Others, as most of the metallic, saline, and organic irritants, kill the cells by precipitating their proteids.

The chemic destruction of tissue is always preceded by this inflammatory necrosis. Chemic cauterization will therefore always show three areas: The first, situated at the depth and periphery of the ulcer, is simply an area of inflammation and hyperemia. Then follows a layer of necrotic tissue, the result of the inflammatory action; and last, a layer in which the chemic cauterization results in solution of the cells which have already been killed by the inflammatory process. These three — hyperemia, inflammatory necrosis, and chemic solution — are to be considered as successive stages in the same action; and by proper dilution, the second or first degree of action may be obtained without the succeeding stages.

The strength of action, for the same substance, is a matter depending on the concentration, rather than on the absolute amount — just as a gram of $MgSO_4$ in solid form introduced into a solution, may precipitate all its globulin, whilst an unlimited quantity may be added in 5% solution, without any such effect.

When the chemic corrosion leads to a loss of substance, the inflammatory exudate will be poured on the surface, where it will coagulate. This coagulum, together with the products of the chemic action of the irritant upon it and upon the cells,— the albuminates, etc., which are formed,— constitute the " scab " or " **eschar.**" Its character will vary with the nature of the chemic products entering into it:

If the irritant has a solvent action on proteids, as is the case with alkalies, the scab will tend to be liquid. If, on the other hand, the combination between the proteid and the irritant is insoluble, as with most metals, the scab will tend to be hard. This is of considerable importance, since it determines the depth of action of the corrosive agent. If the scab is soft, the chemical will penetrate it, and its action will not be limited; it will spread and extend deeply. On this account the alkalies, for instance, are not practical for the purpose of cauterization. If, on the other hand, the scab is solid, it prevents deeper penetration, so that the action can be very easily confined to the desired areas.

In the case of actual destruction of tissue by cauterization, resolution will take place, as after inflammatory necrosis, by scar-formation.

Many drugs cause a *dermatitis* when they are given by mouth (belladonna, arsenic, iodoform, quinin, salicin, antipyretics, iodids and bromids, digitalis, chloral, chloroform, etc.). This is sometimes due to changes in the cutaneous circulation, sometimes to the excretion of the drug by the skin. It may take the form of scarlatinal, desquamating, urticarial or papular rashes or acne.

2. Certain differences in detail will be seen when irritants are applied to other surfaces than the skin; for instance, to the **mucous membranes.** These are readily explained by anatomic peculiarities. There will, for instance, be less tendency to vesication, since the epithelium is not impermeable, as it is in the skin. Nor will there be any chance of the distinct pustulation, which depends upon the cutaneous glands. On the other hand, the mucous glands will be stimulated to an increased activity, producing *"catarrhal" conditions.*

The *tongue* reacts to different forms of mild irritation in a somewhat specific manner, which seems to have its basis in the papillary arrangement. These differences, constituting the various kinds of "coatings," etc., are of some diagnostic importance in disease. But they can all be reduced to the ordinary phenomena of moderate inflammation: hyperemia and proliferation, or necrosis and desquamation of epithelium.. The epithelium of the mouth is sufficiently impermeable to allow of vesication, although less readily than the skin.

In the **stomach and intestine** the action of irritants will produce physiologic as well as anatomic phenomena, comprised under the name of *gastro-enteritis* (see p. 667).

3. Kidney and Liver.— None of the irritants exert their irritant action upon the body at large. Most of them are not at all absorbed, and when absorption does take place, they are too greatly diluted to act anywhere except in the liver, and especially in the **kidney.**[1] All irritant substances will produce nephritis if they are absorbed. Many of them will cause irritation of the liver-cells, leading to fatty degeneration, and later to cirrhosis, precisely as in the case of alcohol.

4. Respiratory Passages.— If an irritant poison is *volatile,* its main effects may fall upon the *respiratory passages.* The general phenomena will be those of acute laryngitis, bronchitis, or pneumonitis.

5. There appear to be some **specific differences** between the different irritants as to the strength of their action in different situations. Some, for instance, seem to act especially on the alimentary canal, and to a very small extent on the skin. This is probably connected with differences of absorbability. A drug which cannot penetrate the skin, cannot, of course, act upon it. It will be remembered that the epidermis is impermeable to most substances. In order to penetrate, these must be either fatty, like croton oil; or volatile, like turpentine; or they must actually destroy the epidermis, like caustics.

All irritant substances will act to some extent as **antiseptics.** They will destroy the protoplasm of bacteria, just as they do that of tissue cells.

Applied to *wounds, ulcers,* etc., the milder irritants cause the destruction of the diseased superficial cells, but stimulate the underlying cells to more rapid division. They consequently promote healing.

II. PHENOMENA OF ASTRINGENT ACTION.

When the solvent action of the chemical is very small and its precipitant action very large, the course of events is quite different from that described. It leads in this case to what is called an *"astringent action."* The astringent action is always preceded by a small amount of inflammatory action. But this, instead of passing on to necrosis of tissue, leads to a diminution of the already existing inflammatory process. An astringent action may be defined as one which lessens the typical processes of inflammation, — that is, the congestion and the permeability of the capillary walls,— and leads to the absorption of the effusion. The astringents also produce a visible *wrinkling of the mucous membranes* to which they are applied, and lessen the secretion of mucus. They possess a peculiar "astringent" *taste.*

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[1] Exercise 33.

Explanation of Astringent Action.— The manner in which this astringent action is brought about is still only imperfectly understood. All astringents produce precipitation of proteids, and this insoluble proteid precipitate seems to be the cause of the astringent action. To explain this action it has been assumed that these precipitates form a lining along the capillary walls, and in this way add an additional coat, as it were, to each capillary. It seems, however, much more likely that they act by coagulating the ordinarily semifluid cement substance between the endothelial cells, and that this prevents the filtration of fluids, and more especially the emigration of cells. The silver "staining" of endothelia by silver nitrate is a visible illustration of this fixation of the cement substance. The diminished mucus secretion is perhaps due to a similar superficial coagulation of the cell envelope. The blanching and puckering (produced only by the more concentrated solutions) points to a direct stimulation of the arterial and other muscular tissue. The *absorption of already formed effusions,* following the use of astringents, may possibly be explained by osmotic laws: By precipitating the proteids of these effusions, they lower their molecular concentration, and render them more diffusible.

The principal astringents are: metallic salts, tannins, dilute acids, and strongly hypertonic solutions. They are used therapeutically to check diarrhea, reduce inflammation of mucous membranes, promote healing, and arrest hemorrhage.

Not all proteid precipitants are astringents. The precipitant action must be of a special kind. It must be produced very quickly, and the precipitate must be practically impermeable to the precipitant. Otherwise the precipitant action would extend so deeply as to lead to extensive necrosis, and would thus continue the inflammatory process. We repeat, that the main essential to astringency is that the precipitate will prevent further penetration of the astringent into healthy tissues. Its action must be confined to the inflamed area — to the place where it is applied. From this it follows that it is absolutely *irrational to expect a remote action from astringents.* The very facts of their action exclude such a possibility. Before this was well understood it was tried to obtain astringent action throughout the body by external application or by giving astringents by the mouth. The want of success confirmed what has just been said.

In the *intestinal canal* the astringents seem to form a deposit along the lumen of the intestine, and in this way prevent absorption, and also the penetration of other irritant substances, in this way lessening peristalsis.

III. GENERAL TOXICOLOGY OF IRRITANTS.

The phenomena produced by irritant poisons will, of course, depend in the first place upon the part of the body with which they are brought into immediate contact. The most prominent symptoms arise from the skin, alimentary canal, or respiratory organs; the last only in the case of very volatile poisons. Later symptoms may appear in the urinary organs.

The extent of the action depends upon the concentration of the poisons, the time during which they act, and the extent of surface with which they come into contact — less upon their absolute amount. If taken by the alimentary canal, their action will also be modified by the presence of food.

1. Cauterization of the Skin.— This may be either accidental or criminal. In the latter case it is usually by sulphuric acid ("Vitriol"). The *results* are the same as in the case of extensive burns. The *diagnosis* offers no difficulty. The character of the stains is that described on page 669. Sufficient of the corrosive can always be collected from the clothing, etc., to establish its identity by chemic means. The *treatment* is precisely like that for burns, after previous neutralization and removal of the corrosive agent. Salves and oils are useful — especially the Linimentum Calcis (Carron Oil, *i. e.,* equal parts Linseed Oil and Lime-water).

2. Poisoning by the Alimentary Canal.— The introduction of caustics by the mouth is almost always either accidental or suicidal. The effects are so painful and appear so promptly, and the lesions are so persistent, that they would scarcely ever be used in criminal poisoning — except possibly in infanticide. They are sometimes taken by mistake for syrup or other medicine, and may be swallowed before the difference is noticed. However, certain organic irritants, usually insoluble, such as croton oil, do not produce their action for some time.

The phenomena vary according to whether the irritant produces an actual cauterization — a destruction or solution of the tissues; or whether it causes only inflammation. We shall begin with the latter class.

(A) **Irritants which do not destroy the tissue:** To this class belong elaterium, croton oil, and most of the other organic irritants, such as volatile oils, etc.

The symptoms are those of a violent **gastro-enteritis:**[1] nausea, vomiting, and diarrhea. If the poison will act only when dissolved, and is insoluble in the stomach, as is croton oil, the nausea and vomiting will not be present, but only the diarrhea. The symptoms will appear correspondingly late. The abdomen is usually distended and extremely painful, especially upon pressure. As a result of the gastro-enteritis, there will be an extensive dilatation of the splanchnic area, and consequently withdrawal of blood from other parts of the body. This will produce marked changes in the circulation. The pulse will be soft, small, and quick. The *lowered circulation* will react upon other organs, and most conspicuously upon the *central nervous system*. There is great anxiety, vertigo, delirium convulsions, then *collapse,* and finally coma and death. This picture is common to the entire series of irritant poisons.

Abortion.— The hyperemia is not confined to the intestine, but extends to all the abdominal organs, which therefore partake in the inflammation, although they do not come into direct contact with the irritant. The most important organ involved in this is the uterus, and the organic irritants have been very frequently used to procure criminal abortion. Oil of savin, of tansy, and of pennyroyal enjoy a special reputation in this connection, but any other irritant produces the same result. The ecbolic effect is only secondary to the gastro-enteritis, and the latter is very often fatal without accomplishing the object for which it was produced.

The *postmortem appearances* are those of gastro-enteritis, and in cases of suspected criminal abortion this must be of sufficient extent to explain the fatal issue. The pathologic condition consists in an intense congestion of the entire alimentary canal, often with inflammatory exudate into the lumen of the intestine. The congestion may be so violent as to produce ecchymoses. If these are present, the vomit and stools will be tinged with blood during life. Destruction of tissue is quite rare. It may, however, occur from gangrene due to the interference with the circulation.

(B) The fixed caustics: The poisons which are of greatest importance in this connection are the mineral acids, and, to a much less extent, carbolic acid; oxalic acid, which, however, stands apart on account of its specific toxic action; the organic acids, which are, generally speaking, corrosive in proportion to their volatility; the alkalies, the alkaline earths, and the carbonates; the haloid substances, bromin, chlorin, and iodin. Metals are also to some extent corrosive, but not usually sufficiently so to produce perforation. The alkalies and bromin produce the most extensive destruction of tissue, because of their deep penetration. With them, the scar-formation is also the most extensive.

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[1] Exercise 32.

All caustics will cause symptoms from the destruction of the tissues with which they come into contact, in addition to the gastro-enteritis. The importance of this lies in the reflex affection of the central nervous system — in **shock** — which may appear so quickly and be so violent as to entirely cover up the local symptoms. Death may occur before vomiting and diarrhea have had time to develop.

Effect of caustics on the circulation.— Sollmann, Brown and Williams (1906) have shown that irritation of the stomach or peritoneum has practically no effect on the blood pressure in anesthetized animals, even when the anesthesia is light. There is generally a marked increase of respiration, and sometimes a slight and momentary rise of blood-pressure, but no fall is noticed for several hours. This holds true both for mild irritants, such as peppermint, mustard or moderate heat; and for strong corrosion by formaldehyd, concentrated acids, or actual cautery, even when these measures produce perforation. It has been shown by the older authors (Gruetzner and Heidenhain, 1877) that strong corrosion of the skin has no effect on the blood-pressure, whilst a mild stimulation, such as blowing, may cause a marked change.

It would seem therefor that the prompt shock, seen so frequently in corrosive poisoning, is psychic, due to the apprehension and pain experienced by the patient. The later collapse may be referable to a more direct action.

A further importance of the corrosive action lies in the fact that it may produce perforation, and consequently peritonitis, and death from this cause. If the poisoning is not immediately fatal, the corrosion will lead to scar-formation, and consequently stenosis, and the patient very frequently dies after a long time from inanition due to the interference of the stenosis with swallowing, etc.

The *acute symptoms* begin in the mouth, with a burning pain, dysphagia, and loss of tissue.

The taste of many of these substances is characteristic — acid, alkaline, metallic, astringent, etc. The nature of the corrosion in the mouth is of great diagnostic importance.[1]

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[1] Exercises 16 and 17.

Alkalies cause a transparent swelling of the epithelium, which will detach as a gelatinous mass, exposing the scarlet-colored inflamed area beneath.[2] The other corrosives, which precipitate proteids, produce at first a grayish-white opaque stain. This persists in the case of the metallic poisons. The acids, however, change the hemoglobin in the neighboring area into the dark acid-hematin, and the color of the stain consequently becomes dark or black. Nitric acid is an exception: its stain takes on a yellow color. This differs from that of picric acid by being changed to orange by alkalies, whilst the picric acid stain remains unaltered. Bromin produces a characteristic light brown or orange stain; iodin stains a mahogany color. The silver stain turns black after a time.[3]

The *esophagus* is also corroded, and ordinarily especially at its beginning and end, and at the place where it crosses the left bronchus.[4]

In the *stomach* the principal corrosions will be found at the pylorus, since the caustic follows the lesser curvature and accumulates at the pyloric end.[5]

The symptoms consist in the gastro-enteritis which has been described. The vomiting and diarrhea are more frequently bloody. In the case of acids the vomited blood is frequently very dark in color on account of the formation of acid hematin. This is the so-called "coffee-grounds" vomit. The pain is very much more marked with corrosive poisons. Death from gastro-enteritis may ensue in from twenty-four to forty-eight hours. The absorption of the products of the chemic action of these agents on the tissues very frequently leads to fever. On the other hand, the collapse may lead to a fall of temperature.

In the *postmortem examination* one would look for evidence of destruction of tissue in the gastro-intestinal canal. This would be found in the upper portions in the case of most of the ordinary corrosive poisons, as acids, alkalies, and haloids; whereas with metals it is often in the cecum or large intestine, because they are excreted in these situations.[6]

When the action has not progressed to actual corrosion, there is often very marked hyperemia and ecchymosis. The color is frequently much darker than corresponds to the amount of congestion, especially in the case of acids (due to acid hematin).[7] Alkalies, on the other hand, have a tendency to make the blood appear lighter.[8]

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[2] E. v. Hoffmann, Atlas of Legal Medicine, W. B. Saunders, 1898. Plate 46.

[3] The stains of iodin and silver are frequently a source of annoyance in the therapeutic exhibition of these. They can be readily removed: The iodin by ammonia water; the silver by potassium cyanid, or by painting first with iodin and then with ammonia (Exercise 17).

[4] ib. Fig. 186 and 187.

[5] ib. Fig. 187.

[6] ib. Plate 43.

The other abdominal organs are also hyperemic.

3. Volatile Caustics.—

These comprise ammonia, chlorin, bromin, the fuming mineral acids, the gaseous acids, such as sulphurous, nitrous, etc.; and certain organic acids — acetic, formic, etc. Also other organic substances, such as formaldehyd; and the volatile oils, especially the oil of mustard.

When swallowed, these produce the symptoms already described, the actions being, however, more rapid and extending more deeply. When inhaled, they irritate mainly the respiratory passages and other exposed mucous membranes, producing coryza, conjunctivitis, bronchitis, pulmonary edema, pneumonia, etc. Through the irritation they produce profound nervous effects, at first mainly stimulant. The respiration stops at first in expiration, the glottis closes spasmodically, and the bronchial muscles contract. This is a conservative mechanism, and explains why fatal poisoning is not more common. During this stage there is cardiac inhibition through vagus stimulation, and also dilation of peripheral vessels. The inhalation irritants may prove promptly fatal by spasm or edema of the glottis; or the course may be slower, passing through bronchitis, pneumonia, etc. The inhalation of irritant vapor is especially deleterious to asthmatic individuals. The effects of *small quantities of volatile irritants in the air* has an economic importance, in view of their escape from chemical factories, etc. There can be little doubt that even a small proportion tends to produce bronchitis, and possibly cachectic conditions; but it is difficult to assign the limits between which these poisons are harmless, objectionable, and dangerous.

4. Treatment of Poisoning by Corrosives.— The first measure is *dilution,* since the action is proportional to the concentration. The drinking of water in abundance and the washing out of the stomach are therefore important. If corrosion is already advanced, it is not advisable to pass the stomach-tube. The further treatment consists in the administration of *demulcent* substances, as mucilage or boiled starch; or proteids, as white of egg; or milk. The proteids are especially useful against the metallic poisons, since they form rather insoluble albuminates.

The pain usually requires the exhibition of *narcotics* in free doses. Most of the irritant poisons can be treated by *chemic antidotes;* in the case of alkalies, by acids; in the case of acids and the haloids, by means of alkalies.

For poisoning by acids or haloids the free alkalies are usually too strong. The carbonates, on the other hand, will develop carbonic acid, and this produces distention of the stomach, and therefore pressure on the already weakened organs, and may even lead to rupture. The carbonates are consequently contraindicated. The potassium preparations in general must be avoided, because, in the corroded condition of the stomach, they would probably be absorbed in sufficient amount to produce potassium poisoning. So the choice is practically restricted to soap or magnesium oxid. Of course, in case of necessity one takes almost anything at hand, such as whitewash or chalk; but magnesium oxid should be preferred. In the case of alkali-poisoning any dilute acid will do, in strength of about 5%. Vinegar will usually be the most handy, but the nature of the acid is immaterial. Poisoning by bromin or iodin is treated with sodium bicarbonate. Caustics in the eye are best washed away by a free supply of water.

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[7] ib. Plate 34, 35 and 33.

[8] ib. Plate 45 and 31.

(B) DETAILS OF THE DIFFERENT CLASSES OF IRRITANTS.

THE ACTION OF WATER AND THE NEUTRAL SALTS

has been described in Chapter XXIV, A. It is a pure physical salt action, leading to mild superficial irritation — mild hyperemia and sensory stimulation. With *water* the action on the intact skin is very small indeed, because the stratum corneum prevents penetration. On denuded surfaces, where the stratum corneum has been removed, the action is considerably stronger. It leads here to the death of the superficial cells, and stimulation of the underlying layers to more rapid multiplication. The action on the stomach and intestine is precisely similar. The latter help to explain some of the beneficial effects of "water-cures" in certain cases of dyspepsia. The action on the skin may be obtained by poultices, compresses, or protracted baths, and may conceivably be of use in some skin diseases. But, as has been said, the action is slight; the effects of poultices and baths are almost exclusively thermal and reflex.

Solutions of *neutral salts* stimulate the skin in a similar manner, but somewhat more profoundly. They penetrate more readily, and consequently produce some stimulation on the intact skin. This is only superficial, but in the shape of sea-water baths it can be made quite extensive, so that salts are especially useful when it is wished to obtain a mild but extensive stimulation of the skin. These salts possess an advantage over most other irritants in that they do not injure the epidermis.

The action of the salts on the stomach and intestine, on the other hand, is rather deep. They are absorbed before they have time to become isotonic, and therefore exert their salt action on all the cells with which they come into contact. They also produce a mild irritation of the renal epithelium. The therapeutic uses of these salts in dyspepsia and as diuretics, as well as their toxicologic importance, and the specific irritant properties of nitrates, chlorates, etc., have been discussed in Chapters XXIV and XXV.

ALKALIES

The group of alkalies includes the free alkalies and those salts which show an alkaline reaction: The carbonates and bicarbonates, borates, sulphids, alkaline cyanids, and basic phosphates.

One must differentiate very sharply between dilute and concentrated solutions.

(a) **Dilute solutions** cause a stimulation of the cells. They soften the epidermis and emulsify and dissolve fat. On the mucous membranes they effect solution of mucus.

Their use in *cleansing the skin* depends upon the emulsification of fat through the formation of soaps, and upon the softening of the epidermis, so that it is readily removed together with the adhering impurities. In the *mouth* the alkalies have a characteristic soapy taste. In the *stomach* the irritant action may be employed to produce some stimulation, and they aid in the solution of mucus. On the other hand, they may derange digestion by neutralizing the gastric juice. Their action is not very deep, since they are neutralized before they can penetrate.

Their irritant action on the *skin* is employed when a stimulation of extensive areas, together with a softening of the epidermis, is desired; as, for instance, in case of ichthyosis. They are then used in the form of alkaline baths.

Any of the alkaline salts can be used; such as sodium carbonate or bicarbonate, potassium carbonate, or borax, in the proportion of about 100 Gm. per bath; for lotions, 2%. These baths are best administered at night, before going to bed.

(b) **Stronger solutions and solid alkalies** combine with the tissue elements to form alkaline albuminates, or with the fats to form soaps, and in this way produce a destruction of substance.

This determines their use as *caustics*. They are also very hygroscopic, and withdraw water from the cells, which contributes to the necrosis. The scab which they produce is very soft, and the compounds which they form are very soluble; consequently the alkalies penetrate very deeply, and it is difficult to circumscribe their action. This is remedied to some extent by mixing them with insoluble powders. A combination of potash and lime makes a fairly useful preparation. But alkaline caustics are quite painful, and lead to extensive scar-formation, so that they are not popular. Only the free alkalies can be used as caustics, since the carbonates are not sufficiently powerful.

(c) **Ammonia** differs from the other alkalies in penetrating deeper, on account of its greater volatility. It passes through the stratum corneum of the epidermis without injuring it, and, acting upon the lower layers of the skin, produces blisters. It is sometimes used for this purpose instead of cantharides, especially in nephritis, where the latter cannot be employed. It is, however, more painful.

It is frequently used in more dilute form as liniment for counterirritation, when a deep action is desired. Its use as a reflex nervous stimulant has been sufficiently discussed. (See p. 561).

THE SULPHUR COMPOUNDS.

The group of sulphur compounds comprises *sulphur, sulphuretted hydrogen,* the *sulphids* and *polysulphids* and *thiosulphate. Ichthyol* and *Thiol* can probably be placed in the same group.

Locally these act as *mild irritants.* H_2S behaves rather like acids. The sulphids and polysulphids are readily decomposed into H_2S and the alkali, so that they exhibit both actions.

Sulphuretted Hydrogen.— The actions of this poison are described on page 461. It is frequently formed in intestinal putrefaction, giving rise to diarrhea. It may be removed by the administration of bismuth salts, and its further formation checked by cathartics and intestinal antiseptics.

The gas is contained in small quantity in a number of mineral waters (sulphur springs). These are recommended for a variety of obscure disorders — rheumatism, gout, diabetes, etc. When these waters are administered for some time, they cause diuresis and diaphoresis, irritation of the urinary passages, intestinal irritation, and muscular pains. Their therapeutic effects are probably to be referred to their laxative, diuretic and diaphoretic actions, although the general hygienic conditions must contribute largely to the results, as with other mineral waters (Boecker, 1895).

Alkaline Sulphids.— When applied to the *skin,* the sulphids produce a softening of the stratum corneum, very much like the alkalies, and they are used in the same conditions. Their action on hair is even greater, so that they are valuable as depilatories, especially calx sulphurata. When taken by *mouth,* they act as corrosives and irritants, through the liberation of sulphuretted hydrogen and free alkali. They produce but little systemic action, as they are rapidly oxidized. They are *excreted* in the urine mainly as sulphates; but there seem to be also some organic sulphur compounds.

A small amount of some volatile sulphur compound is also excreted by the *lungs,* giving the peculiar H_2S odor to the breath, and causing some *expectorant action.*

When injected *intravenously,* the sulphids produce violent convulsions, followed by depression of the medullary centers. This is due to a direct action. Outside of the body, sulphids form a peculiar compound with hemoglobin, but this does not occur during life, in mammals.

Therapeutic Uses: The sulphids are only used externally, in skin diseases, scabies, etc., generally as baths, containing 30 to 200 Gms. (1 to 6 ozs.) of sulphurated potash.

The sulphids have been proposed as an *antidote for hydrocyanic acid,* since they would form sulphocyanids, which do not have the hydrocyanic acid action. This has not been tested. It is possible that the reaction goes on too slowly to be of value.

Sulphur.— Free sulphur, as such, has no action whatever; it is, however, *converted partly into sulphids* in the body, and shares their actions. This conversion takes place on the skin, by the cutaneous secretions. A considerable amount (to 10%) also undergoes this change in the intestine, as may be readily seen from the increased secretion of sulphate by the urine. The conversion is ordinarily referred to the alkalies of the intestine; but Heffter (1904) points out that the alkali exists as bicarbonate, which cannot affect the conversion. He shows that it is produced by proteids of all kinds (even after these are boiled).[1]

The conversion always occurs slowly, so that the actions of sulphur are *gradual, mild and prolonged.* This determines its value. Indeed the flowers of sulphur are more valuable than precipitated sulphur, since the latter is converted too rapidly, on account of its fine subdivision.

The actions of sulphur agree qualitatively with those of the sulphids. On the skin, it acts as a very mild irritant, and is used (as sulphur ointment) mainly as a parasiticide, especially in scabies. By the mouth, it acts as a laxative, softening the stools with practically no intestinal irritation. It is especially valuable in hemorrhoids. It is usually administered as Pulv. Glycyrrhizae Comp.; or mixed with equal parts of cream of tartar.

Organic Sulphur Compounds.— Peculiar value has been attributed to the incompletely oxidized sulphur occurring in organic compounds. The pioneer product of this kind is *ichthyol,* which contains 10% of sulphur as sulfons, mercaptans and sulphids. It is weakly antiseptic and mildly irritant. Taken internally, it produces gastro-intestinal irritation, with diarrhea. Its influence on metabolism is in dispute. It has been *used locally* to cause absorption of swellings and effusions, in contusions, burns, etc., and especially in gynecologic practice. It has also proven useful in skin-diseases, acting somewhat like sulphur. *Internally,* it has been endorsed against the greatest variety of diseases of digestion, respiration, genito-urinary tract, tuberculosis, etc. These claims bear the stamp of exaggeration.

Ichthyol Substitutes.— The disagreeable odor and taste of ichthyol cannot be disguised by flavors, but can be removed by combination: *Ichthalbin,* a compound with albumen, is recommended for internal administration; *Ichthyoform,* an almost insoluble compound with formaldehyde, as antiseptic dusting powder.

The commercial success of ichthyol has led to the substitution of a number of *synthetic products,* formed by saturating mineral oils with sulphur. *Thiol* and *Tumenol* are the principal products of this class. They have the same actions as ichthyol, with the advantage that they are tasteless. Linseed oil saturated with sulphur has long been used in domestic medicine under the name of Harlem Oil.

Sulphites and Sulphurous Acid.— These have some practical importance, as they are used for preserving food. The free acid is very irritant. It is formed by the combustion of sulphur and is used for disinfecting rooms, etc. Sodium sulphite is quite toxic when injected subcutaneously or intravenously, causing depression and paralysis of the central nervous system, especially the medulla; and of the cardiac and arterial muscle. Death occurs by paralysis of respiration. Much larger quantities are tolerated by the mouth; the sulphite being probably slowly absorbed. The greater part is oxidized to the harmless sulphate during and after absorption. Large amounts may cause irritation and vomiting, sulphurous acid being liberated in the stomach. The quantities which may be taken in preserved food cause no symptoms, even when continued for several months. If, however, the animals are killed and examined, extensive hemorrhagic and inflammatory lesions are found in various organs (Kionka and Ebstein, 1902)

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[1] Exercises 19, A, 7.

These are probably due to destruction of red blood cells, with infarction. Harrington, 1904, also describes nephritic changes. The use of these preservatives, except in minimal quantity, should therefore be condemned.

Hyposulphites (really thiosulphates) seem to have similar actions, as far as they have been investigated.

Therapeutic Uses.— Sulphurous acid and sodium sulphite are sometimes used internally in fermentative dyspepsia. The sulphite and thiosulphate (hyposulphite) are employed as mouth-wash in aphthæ, and as 10% lotion in ringworm and other parasitic skin-diseases. The thiosulphate is the more powerful. The weak antiseptic action is due to the reducing property.

MATERIA MEDICA OF SULPHUR COMPOUNDS.

Sulphur Sublimatum (U.S.P., B.P.).— (*Flowers of Sulphur.*)— S. The sublimed crude sulphur. *Dose:* 1 to 4 Gm. (15 to 60 grains). (4 Gm. = 60 grs. U.S.P.) Insoluble.

Sulphur Lotum (U.S.P.)—*Washed Sulphur.*— Sulphur washed with ammonia water, to remove free acid. *Dose:* same.

Enters into the preparation of:

Unguentum Sulphuris (U.S.P., B.P.)— 15%. (Benzoinated Lard.)

Pulvis Glycyrrhizæ Compositus (U.S.P., B.P.).— Contains 8% (10% B.P.) of sulphur. *Dose:* 4 to 8 Gm. (1 to 2 drachms). (4 Gm. = 13, U.S.P.)

Sulphur Precipitatum (U.S.P., B.P.).—(Lac Sulphuris, Milk of Sulphur.)— Made by precipitating a solution of sulphurated lime with HCl. *Dose:* 1 to 3 Gm. (15 to 45 grains). (4 Gm. = 60 grs., U.S.P.)

Calx Sulphurata (U.S.P., B.P.).— Made by reducing Calcium Sulphate by heating with charcoal. Contains 60% of CaS, and is sometimes called "calcium sulphide." It has some repute as checking the formation of boils, being given in *doses* of 0.005 to 0.05 Gm. (1/100 to 3/4 grain). (0.065 Gm. = 1 gr., U.S.P.)

Potassa Sulphurata (B.P.).—(*Liver of Sulphur.*) Made by fusing S and K_2CO_3. Soluble in 2 parts of water. Used in the form of baths (30 to 200 Gm. per bath).

Acidum Sulphurosum (U.S.P., B.P.).— See Index.

Sodii Sulphis (U.S.P., B.P.).— $Na_2SO_3 + 7H_2O$. Sol. in 2. water, sparingly in alc. Oxidizes in air to sulphate. *Dose:* 0.3 to 2 Gm. (5 to 30 grains). (1 Gm. = 15 grs., U.S.P.)

Sodii Bisulphis (U.S.P.).— $NaHSO_3$. Sol. in 3.5 water, 70 alc. *Dose:* as the preceding. (0.5 Gm. = 7½ gr., U.S.P.)

Sodii Thiosulphas (U.S.P.).—(*Sodium Hyposulphite*).— $Na_2S_2O_3 + 5H_2O$. Large crystals, sol. in 0.35 water, insol. in alc. Decomposed by heating. *Dose:* as the Sulphites.

For use as lotions these salts are dissolved in 8 to 10 parts of water.

**Ichthyol:* A mixture of sulphur compounds, obtained by the distillation of a bituminous shale, rich in the fossil remains of fishes (hence the name), found in Tyrol. Rendered soluble in water, glycerin, oils, and equal parts of alcohol and ether, by being partly converted into ammonium ichthyosulfonate. This, the commercial product, is a dark brown oil, of weakly acid reaction, and of disagreeable odor and taste. It is used as ointment, diluted with petrolatum or glycerin, in strengths of 5 to 50%; as a lotion (5 to 10%); or internally in *doses* of 0.2 to 1 Gm. (3 to 15 grains).

****Ichthalbin*** (Ichthyolalbuminate): Brown powder, odorless, insoluble in water, soluble in alkaline fluids. *Dose:* 0.5 to 2 Gm. (8 to 30 grains).

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* *Ichthyoform* (Ichthyol-formaldehyde): Blackish-brown powder, almost odorless; as dusting powder. *Dose,* for intestinal antisepsis, 0.5 to 2 Gm. (8 to 30 grains).

* *Thiol.* An artificial product, consisting mainly of sulfons. Brown oil or powder, odorless, freely soluble in the same solvents as ichthyol. Used in the same manner.

* *Tumenol:* Another similar product. It exists as tumenol proper, a thick oil; as tumenol powder, and as tumenol oil, a thinner product. All are dark-colored and almost odorless. Tumenol and the powder dissolve like ichthyol. The oil is insoluble in water, but soluble in ether. These products are used like ichthyol.

ACIDS.

(For the *Materia Medica* of acids, see Index.)

(a) Members.— The most typical acids in regard to the local action are *sulphuric* and *hydrochloric acid. Nitric* acid produces the same effects, but differs from these in its chemic action, producing xanthoproteic acid from the proteids. The *sulphurous acid* has also a marked corrosive power. *Hydrofluoric acid* has a specific toxic action, penetrates very deeply in virtue of its volatility, and is especially strongly corrosive. Of the *organic acids,* those of the fatty series act similarly, but are weaker. The *trichlor-acetic acid* is the most corrosive of these. The volatility of most of the fatty acids makes them more penetrating than the mineral acids. *Oxalic acid* occupies a place by itself on account of its specific toxic action, produced probably by the precipitation of the calcium.

The *compound acids* — such as ethyl-sulphuric, etc.— act like organic acids. The *aromatic acids* act partly as acids, but this action is greatly obscured by their collapse action.

The irritant action of the acids is also shared to some extent by the *acid salts,* acid tartrates, acid sulphates, etc.

(b) The **nature of the caustic action** produced by acids varies to some extent with the constituents of the tissues. But, on the whole, it consists, with concentrated acids, in withdrawal of water; in the formation of acid albumins; in softening of the connective tissue and epithelium; and in special situations, in solution of calcareous material.

All the concentrated acids have an affinity for water, and withdraw this from the cells. This affinity is so strong in the case of concentrated H_2SO_4 that not only the formed water is withdrawn from the tissues, but the elements H and O are split off from their chemic combinations with carbon, leading to carbonization.

All acids convert *proteids* into acid-albumins, which are insoluble in moderately strong, but soluble in concentrated or very weak acids. Upon this precipitation of proteids depends their astringent and styptic action.

The *connective tissue* undergoes a rather peculiar change. It is not dissolved, but is softened and rendered more soluble in boiling water. (This explains why meat becomes more tender on keeping.) The concentrated acids have a similar effect upon *epithelium.* Without actually dissolving it, they soften it in such a manner that it is readily detached. Dilute acids, on the other hand, harden it.

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* Not official.

The profound tissue destruction by acids gives rise to extensive scar-formation.[1] For this reason, and because they are very painful, they are not much used as caustics.

The destruction of proteids makes acids efficient antiseptics. Even quite dilute solutions, such as the gastric juice, suffice to limit the growth of bacteria. The concentrated acids destroy them outright.

(c) **Dilute solutions** of acids produce a mild irritation, and at the same time harden the epithelium, without destroying it. They are therefore preferred to alkalies as counterirritants.

They differ from the volatile organic irritants in that they do not penetrate so deeply, and do not cause nephritis. They are therefore specifically indicated in certain conditions.

For this purpose they may be used in the form of baths, in the strength of about 30 c.c. (1 ounce) to the bath (30 gallons). Or they may be applied as lotions. In this case the volatile acids are preferred, because their action is deeper. Formic acid has a special reputation. It is used in the strength of about 4% or 5% in alcohol.

This stimulation of the skin without destruction of epidermis is very frequently used to increase the amount of sweat; and acids, usually in the form of vinegar, are therefore used for sponging in fever. On this account they have received the name of "refrigerants." On the other hand, they are used in excessive secretion of sweat (sweating feet) to harden the epidermis. For this purpose 5 or 10 c.c. of concentrated hydrochloric acid are put in a basin of water and the feet placed in this until they become painful. This is done about twice a week.

Their use in dyspepsia has already been noted on page 585. The continued use of even quite dilute solutions of mineral acids (mineral lemonade) leads to chronic gastritis. The irritant action on the alimentary canal is employed to produce catharsis. It has been pointed out (Chap. XXVI) that the free acids will not *reach the intestine*, so that acid salts or acid fruits are used for this purpose.

The irritant action of the volatile acids is sometimes employed to produce reflex stimulation of the central nervous system by inhaling vinegar, etc.

(d) **Continued exposure to the vapors of acids**, as occurs in certain trades, gives rise to chronic bronchitis. They also attack the teeth, and from these the necrosis may spread to the jaw, as with phosphorus.

THE HALOIDS.

(a) **General.**—These comprise *bromin*, *iodin*, *chlorin*, and the *hypochlorites*.

Their corrosive action is determined by their entering very easily into chemic reaction with all kinds of organic substances, taking from them hydrogen and forming hydrobromic, hydrochloric, and hydriodic acids, which have the ordinary acid actions. If water is present they will set free oxygen in the form of ozone, by combining with the hydrogen of the water; this is also a strong irritant. The halogens furthermore enter directly into the proteid molecule.

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[1] See v. Hoffmann's Atlas of Legal Medicine, Plates 33, 34, 35, 36 and 37.

(b) Bromin and Chlorin.—*Bromin* is the most violent of the haloids, because it is at once volatile and fluid. It produces very deep and very extensive destruction of substance, somewhat like alkalies.

As volatile poisons, *bromin* and *chlorin* have a very strong action upon the respiratory organs. One part in a million of bromin is already disagreeable; 10:1,000,000 is said to be dangerous.

The action of bromin and chlorin is purely local.

It has been claimed that they are absorbed and excreted in the free state in the urine. The absurdity of this is shown by the fact that these are used as tests for urea.

Bromin, chlorin, and the hypochlorites are sometimes used as antiseptics. (See Chap. XVII, C.) They have practically no other therapeutic uses.

(c) Iodin.—The case is quite different with the remaining haloid, *idoin*. Free iodin forms one of the most useful of counterirritants. Just as in the case of the iodids, however, its characteristic action has in it nothing special, but can be explained on easily understood principles. It precipitates proteids and enters into easily dissociated compounds with them. On this account it remains for a long time at the place where it is applied. At the same time, it penetrates on account of its volatility. Its action is therefore at once lasting and penetrating. The action is comparatively mild, and can be easily graduated by successive applications; so that it is possible to reach very strong sensory irritation without causing a deep destruction of tissue.

These actions suffice to explain its **therapeutic** success. It is used mainly for the removal of *inflammatory products*: in *rheumatism*, *tubercular glands* and swellings, *syphilitic* affections, etc. It was at one time used extensively by injection to cause **adhesive inflammation** in cysts of all kinds. This is extremely painful, and sometimes causes local gangrene, or at times enough is absorbed to cause general symptoms: gastritis, arterial spasm, neurotic conditions, solution of red corpuscles, degenerative lesions in the liver, etc. If it is used at all for injection, it should be in the form of the compound (aqueous) solution (Lugol's solution) and not of the alcoholic tincture. It has been displaced almost entirely by surgical treatment. In its injection in *goiter* it probably acts simply as a counterirritant, and not as do the iodids given internally.

The *treatment of poisoning* by haloids consists in demulcents (egg or milk or oils); dilute alkalies ($NaHCO_3$); iodin demands starch. Sodium hyposulphite is also somewhat antidotal.

MATERIA MEDICA OF HALOIDS.

Bromum (U.S.P.).—Br. A brown liquid.

* **Chlorum.**—Cl. A green gas.

Liquor Chlori Compositus (U. S. P.).—(*Aqua Chlori*). At least 0.4% Cl. Should be freshly made by decomposing $KClO_3$ with HCl. *Dose:* 4 c.c. = 13 (U. S. P.

Calx Chlorinata (U. S. P., B.P.).—*Chlorinated Lime.*—(*Bleaching powder.*) (Miscalled Chloride of Lime.) Made by passing chlorin over slaked lime. Should contain 30% of chlorin which can be liberated by acids.

Liquor Sodæ Chlorinatæ (U.S.P., B. P.).—*Labarraque's Solution* Javelle Water.—Made by decomposing Chlorinated Lime with a solution of Sodium Carbonate. Contains at least 2.4% of Chlorin. *Dose:* 1 c.c. = 15 ♏, U.S.P.

Iodum (U.S.P., B.P.).—*Iodin.*—I. Characteristic scales; soluble in 5000 water, freely in aqueous solution of KI or in 10 parts of Alcohol. *Dose:* 5 mg. = $^1/_{10}$ gr., U.S.P.

Liquor Iodi Compositus (U.S.P.).—(*Lugol's Solution.*)—I, 5%; KI, 10%. *Dose:* 0.06 to 0.5 c.c. (1 to 10 minims). (0.2 c.c. = 3 ♏, U.S.P.)

Liquor Iodi Fortis (B.P.).—14% I in KI. Externally.

Tinctura Iodi (U.S.P., 7%; KI, 5%) [B.P., 2½%]. *Dose:* 0.06 to 0.3 c.c. (1 to 5 minims), diluted. (0.1 c.c. = 1½ ♏, U.S.P.)

Unguentum Iodi (U.S.P., B.P.).—4%.

Sulphuris Iodidum (U.S.P., B.P.).—Made by fusing sulphur and iodin. Contains 80% of the latter. Used externally like iodin.

Unguentum Sulphuris Iodidi (B.P.).

* *Iodin Tribromid.*—IBr_3. Recommended in angina diphtheritica as spray, in 1:300 dilution.

* *Iodin Trichlorid.*—ICl_3. Antiseptic (1 : 1000). Soluble in alcohol.

(d) Iodoform.—This substance acts by liberating iodin; but this shows some peculiarities, due to the manner in which it is produced. Iodoform itself is insoluble and probably quite inactive. It is also quite stable outside of the body; but in contact with tissues or their extracts, and particularly with diseased tissues and with bacteria, it slowly *evolves iodin* (Altenburg, Schmidt, 1901). This occurs so slowly that the effects are mild, but quite sufficient to be markedly antiseptic to bacteria, and stimulant to the cells. Iodoform is therefore very valuable in treating open wounds, since it promotes healing by stimulating granulation and lessening or preventing infection. It is the most universally used dusting powder; it is also injected into tubercular joints, usually as an emulsion with glycerin (see page 387).

Iodoform has, however, a number of *disadvantages:* The most objectionable feature is the persistent odor, which cannot be disguised by any perfume. Iodoform is also apt to develop irritant phenomena in susceptible individuals, producing particularly *eczemas,* even in minute amounts.

General Intoxication.—(P. Mulzer, 1905). This may occur when iodoform is applied over a large area, or when it is injected. The symptoms consist in diuresis, lassitude and somnolence, hallucinations, diminished reflexes, light convulsions, and paralyses. The temperature falls. Death occurs through general paralysis of the central nervous system. Sodium bicarbonate is said to be antidotal. *Chronic poisoning* is also characterized by paralytic phenomena. The heart, liver and kidneys exhibit fatty changes. Iodoform dermatitis is sometimes seen. It resembles ivy poisoning (Bryan, 1903).

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* Not official.

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Excretion: Iodoform is not excreted as such, either by the kidneys or lungs. It appears in the urine as iodid and iodate.

(e) Iodoform Substitutes.— The unpleasant odor of iodoform has led to a search for substitutes. The odor can be much diminished by combining the iodoform with hexamethylenetetramin ("*Iodoformin*") and this with ethyl-iodid ("*Iodoformal*"); or by enveloping the iodoform with coagulated proteid ("*Iodoformogen*"). All these compounds, however, are decomposed by water, with the liberation of iodoform; so that they accomplish their object very imperfectly.

Since the value of iodoform rests on the slow evolution of iodin, it could theoretically be replaced by other inodorous, insoluble compounds holding iodin in weak combination. A number of such products have been introduced. Although it is not easy to form a fair judgment of their value, they seem to be rather inferior to iodoform. It is apparently very difficult to reproduce just the same favorable loose combination. The high price of these products is also against them.

The following are the principal, more or less successful, iodoform substitutes of this class:

Thymol Iodid (Aristol), *Iodol* (tetra-iodo-pyrrol); *Europhen* (a cresol iodid); and *Eigon* (iodized proteid). These may also be used internally for the systemic effects of iodin, but have no advantage over potassium iodid. *Diiodoform* (C_2I_4) has also been tried as iodoform substitute, but decomposes too readily.

Iodin introduced into the nucleus of benzol-derivatives is held so firmly that these compounds do not have the iodoform action — although they are generally antiseptic by belonging to the benzol-series. Such products are: *Losophan* (Tri-iod-metacresol — very irritant, used against cutaneous parasites); also tetra-iod-phenolphthalein (*Nosophen*) and its sodium salt (*Antinosin*) and bismuth salt (*Eudoxin*); *Sozoiodol* and *Picrol* (iodized aromatic sulfo-acids), etc.

Some of the indications of iodoform may be met by ***bismuth salts*** (see page 620).

MATERIA MEDICA OF IODOFORM GROUP.

Iodoformum (U. S. P., B. P.).— *Iodoform.*— CHI_3. Made by the reaction of alcohol, iodin, and pot. bicarbonate. Yellow crystals of a characteristic odor. Very slightly soluble in water or glycerin, soluble in 46.7 parts of alcohol, freely in oils or ether. Contains 97% of iodin. *Dose:* 0.05 to 0.2 Gm. (1 to 3 grs.) (0.25 Gm.=4 grs., U. S. P.).

Unguentum Iodoformi (U. S. P., B. P.) contains 10%, in Lard.

Suppositoria Iodoformi (B. P.) each contains 0.2 Gm. (3 grs.)

Iodoform (and other loose iodin derivatives) are ***incompatible with starch.*** They are generally ***decomposed by heat,*** and can therefore not be sterilized in this manner. Since they become antiseptic when applied to wounds, sterilization is usually superfluous. Iodoform rendered aseptic by the addition of a trace of paraform is on the market under the name of "Eka-iodoform."

The ***iodoform substitutes*** are also injured by heat and light. They are all insoluble in water and are used like iodoform.

* *Iodoformin*, *Iodoformal*, and *Iodoformogen* have a faint odor of iodoform; the first is whitish, the others yellow. The first two liberate

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iodoform on the addition of water. Iodoformin contains 75% of iodoform; iodoformogen 10%.

Thymolis Iodidum (U. S. P.).— (Dithymol-diiodid — $(C_6H_2CH_3.C_3H_7.OI)_2$ — *Aristol*).— Contains 45% Iodin. Chocolate colored powder with slight aromatic odor. Insol. in water or glyc.; slightly sol. in alc., readily in oils, ether, etc.

Iodolum (U. S. P.).— *Iodol* — Tetraiodopyrrol — $C_4I_4.NH$. Grayish-brown powder, without odor or taste. Sol. in 4900 water, 9 alc.; also in oils, etc. *Dose:* 0.25 Gm. = 4 grs. (U. S. P.).

* *Europhen, Eigon, Diiodoform.*— Yellow powders, practically devoid of odor and taste.

* *Losophan* occurs as white, odorless needles, practically insoluble in water; used as 1 to 3% ointment or 1% lotion (with 75% alcohol) in ringworm, favus, pruritus, etc.

* *Nosophen and Eudoxin* are brownish powders, practically insoluble in water, used on wounds, and internally as intestinal antiseptics in *dose* of 0.3 to 0.5 Gm. (5 to 10 grains).

* *Antinosin* occurs as blue crystals, soluble in water, used as antiseptic lotion in strength of 0.1 to 2%.

* *Sozoiodol* (Di-iod-phenol sulfoacid) is used as antiseptic in the form of its Hg, K, Na and Zn salts.

HYDROGEN DIOXID.

The peroxids resemble the halogens somewhat. They are fairly stable, but under certain conditions they part with a portion of their oxygen, which in this nascent condition is especially active, and exerts antiseptic effects. The hydrogen peroxid is the best known and is employed for washing wounds and ulcers, as injection for gonorrhea, as mouth-wash, etc. It is scarcely irritant, but is best diluted. In contact with pus it foams, and this aids mechanically in cleansing the wound. Hydrogen peroxid is also a chemic antidote for cyanid and phosphorus poisoning. It is often used for bleaching the hair and fabrics.

Aqua Hydrogenii Dioxidi (U. S. P.) (*Liquor Hydrogenii Peroxidi*, B. P.).— An aqueous solution containing 3% by weight of H_2O_2, and yielding ten times its volume of oxygen. (Prepared by decomposing barium peroxid by means of phosphoric acid. Incompatible with easily oxidizable substances.)

* *Pyrozon* represents a 50% solution of H_2O_2 in ether.

The *organic peroxids,* which are used as intestinal antiseptics, are discussed on page 386.

METALLIC SALTS.

(a) General.— The local action of metallic salts (with the exception of arsenic and antimony) is due to their forming compounds with the tissue elements, which are only soluble under certain conditions. In this way the albuminate, etc., of the metal is formed, and the acid of the metallic salt is set free. If, for instance, a solution of ferric chlorid is added to egg-albumen, the result is an albuminate of iron, and free hydrochloric acid.

This free acid will exert its own irritant action. So that the local effects of metallic salts rest on two factors: the precipitant action of the metal, and the irritant action of the liberated acid. Both will have an influence upon the total effect. The metal-proteid compounds are usually of inconstant composition; *i. e.*, they contain varying amounts of metal and proteids.

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*** Not official.**

Some of these metal albuminates are almost insoluble in water; some are soluble in excess of proteid, especially when neutral salts are present; others are not. This solubility is of practical importance in the local action. If the precipitate is soluble, there is no obstacle to the penetration of the metal, and its action, irritant or caustic, is deep. If, on the other hand, the precipitate is insoluble, as in the case of lead salts, penetration cannot take place; the irritation is confined to the surface, and an astringent action results. The difference between caustic and astringent action is therefore mainly one of penetration. In regard to this, the metals stand in about the following order: The most astringent is lead; then comes aluminum; then iron; then zinc, copper, silver, and tin, which stand about on a level; the most caustic is mercury. As to the liberated acids, the strongest caustic action appears in hydrochloric acid; then comes nitric acid; then sulphuric; then phosphoric; the weakest of all are the organic acids — acetic, citric, and tartaric.

By proper combination, then, between the metals and the acids, one may obtain any grade of action from pure caustic to pure astringent.

The most typical caustic would be mercuric chlorid, the most typical astringent, lead acetate.

The strength of action will, of course, also depend upon the concentration in which the salt is used, and this is often limited by its solubility. The chlorid of silver would, theoretically, be a stronger caustic than the nitrate, but since it is not soluble, it cannot be used in the same concentration.

It must not be forgotten that the irritant action, the astringent action, and the caustic action, are merely degrees of the same process. The astringent action always precedes the caustic action; and, consequently, by proper dilution, one may obtain astringent effects from salts which are ordinarily purely caustic. For instance, silver nitrate can be so graduated in strength as to have a purely astringent action, without any caustic effect whatever.

It is therefore impossible to establish a perfectly definite classification between the metallic salts. An approximation to it is given in the following table:

CLASSIFICATION OF METALLIC SALTS.

Mainly Caustic: All Hg salts; $ZnCl_2$; $SnCl_4$; $SbCl_3$;
tartar emetic; $CuSO_4$.
Both Caustic and Astringent: Fe salts; $ZnSO_4$;
$ZnAc_2$*; $CuAc_2$; $AgNO_3$; $Pb(NO_3)_2$; PbI_2.
Mainly Astringent: Alum; $PbAc_2$; Pb_2OAc_2; ZnO.
Bi subnitrate; white precipitate.

(b) *The* **caustic action** *of metallic salts:* This was formerly used quite extensively, but it has now been largely abandoned. Most are not sufficiently powerful for this purpose; others, again, are too toxic, being absorbed in sufficient amount to produce poisoning. To the latter class belong arsenic, antimony, and mercury. Zinc chlorid and antimony chlorid (Butter of Antimony) are very active caustics, but rather too diffluent. Their scab is so soft that their action cannot be kept within bounds. In fact, of all the metallic caustics, silver nitrate in the form of sticks (Lunar Caustic), and to a less extent copper sulphate, are alone used to produce a purely caustic action. *Arsenic,* were it not for its toxicity, would be a very useful corrosive. Its action is so slow that it can be very readily limited. It was believed to destroy only pathologic formations, leaving healthy tissue intact.

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* Ac = Acetate.

This would be easily understood, from the fact that the former are much less staple. *Silver Nitrate* is also quite easily controlled, since its action may be stopped at once by washing with NaCl, which converts it into AgCl.

(c) Irritant Action of Metallic Corrosives.— (a) On the Intact Skin.— The changes produced by metals are too profound to admit of their employment over large areas, or for a long time. They are most extensively used for local counterirritation; for instance, to cause the absorption of inflammatory effusions, or in certain skin diseases. In the latter, they may be valuable largely on account of their antiseptic action.

Mercury is the strongest, both as regards the irritant and antiseptic effects. It may be used as solutions of corrosive sublimate 1 : 10,000 to 1 : 1000; or as the black or yellow wash, (see p. 646); or in the form of ointments. The strength of action of the official ointments is about as follows:

The most irritant and caustic is *Ung. Hydrargyri Nitratis* (Citrine Ointment). Then comes *Ung. Hydrarg. Ammoniat.; Ung. Hydrarg. Oxidi Flavi; Rubri;* least irritant is the *Unguentum Hydrargyri.*

Of other irritant metallic salts, the *Tartar Emetic* is sometimes used in the form of ointment (5 to 10%) to produce pustular eruptions. It is too painful to be popular.

(b) For the use of these irritants on **ulcers** and **mucous membranes,** see Index; their use as **antiseptics,** Chapter XVII, C.

(c) On the Intestinal Canal.— The first effects of the irritant action in this situation are *nausea* and *vomiting.* This is produced by all soluble metallic salts in large doses. But *Copper* and *Zinc* have a rather specific action, irritating the nerve endings which give rise to the reflex of vomiting, and thus being evacuated before they have time to produce any injury.[1] The dose is therefore almost immaterial, within quite wide limits.

Very large doses may not be completely evacuated and may then cause fatal gastro-enteritis — 40 Gm. of $CuSO_4$ proved fatal on the fourth day. The average emetic dose of these salts is about 1 Gm. (15 grains), dissolved in a glass of water, and repeated in fifteen to thirty minutes if necessary. The effect is very prompt and is accompanied by very little nausea. They are therefore more useful as pure emetics than they are as nauseants. Alum is also given in the same way in doses of 4 to 8 Gm., but is not as quick. Tartar Emetic was formerly much used for this purpose. It causes a more prolonged nausea and is more depressant. Its indications are consequently more those of an expectorant. It should not be used continuously for fear of chronic poisoning.

Certain irritant metallic salts do not, in therapeutic doses, develop much action until they reach the **intestine.** Here they act as cathartics.

The most useful of these are the salts of mercury. Mercurous chlorid — *calomel* — deserves the preference, since it is entirely insoluble in the stomach and so avoids the gastric irritation which accompanies the action of all soluble metallic salts. Its solution in the intestine is due to its forming albuminates which are soluble in the mixture of carbonates and chlorids of the intestinal juice. This is the reason why calomel is less actively cathartic in sucklings than in adults: the intestinal canal of the former contains much less chlorid.

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[1] Exercise 30.

This solution is a slow process, so that it has not usually progressed very far when the excess is removed by the catharsis. The dose is therefore immaterial within rather wide limits — from 0.005 to 1.0 Gm.; and even much larger doses were popular with the old-style physician. These are, however, entirely superfluous, and may become dangerous should conditions be exceptionally favorable to solution. This may occasionally occur.[1] When larger doses are employed, it is usual to mix them with small amounts of vegetable cathartics to hasten their evacuation. Podophyllin (5 mg = $^1/_{12}$ gr.), is useful for this purpose. The Pil. Cathart. Comp. of the U.S.P. contains the calomel in serviceable form.

Mercury was formerly considered to stimulate the flow of bile. The fallacy of this has been discussed on page 643.

However, calomel has an advantage over most other cathartics in being distinctly antiseptic, without interfering with the action of ferments. Salts of other metals have also been used as purgatives; thus sulphuret of antimony (Plummer's Pill). Arsenic has a cathartic action, but presents too great danger of toxic effects from absorption.

(d) On Kidneys: A mild degree of the irritant action on the renal epithelium — common to all absorbable metals — leads to a diuresis. This is utilized in practice only in the case of calomel, especially in cardiac dropsy.

Calomel Diuresis.— The diuretic effect of calomel in cardiac dropsy is said to have been well known to the physicians in the latter half of the eighteenth century, but it was forgotten, and practically rediscovered by Jendrássik in 1886. He found it effective mainly in cardiac dropsies, in which it produced results far greater than could be obtained with digitalis or caffein. The urine was often increased to 7 or 8 liters a day. The absolute amount of urea and chlorids was also greatly increased. To obtain the best effects, 0.2 Gm. was given from 4 to 5 times a day, until a slight mercurial stomatitis was produced. If this did not prove effective from the start, the remedy was discontinued; it also seems wise to intermit it occasionally. The bowels may be regulated by opium. Jendrássik remarks that the calomel appears relatively or quite ineffective when the heart disease is uncomplicated by dropsies; it was also ineffective in pleuritic exudates, in nephritic effusions, and in healthy individuals. This report gave rise to extensive trials of the drug. The results of these were summarized by Jendrássik in 1891, together with further observations and experiments of his own. His previous conclusions concerning the best method of administration, and the usefulness of calomel in cardiac dropsies seem to have been generally confirmed, as also the relative insufficiency in non-dropsical heart disease, in pleuritic exudates and in normal individuals. It seemed to be slightly diuretic in the latter, but the action can never compare with that seen in cardiac dropsies. It was often found effective in hepatic ascites, but failed frequently. It gave good results in some cases of nephritic edema, but in most instances gave no result; it seemed impossible to predict what it would do.

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[1] Calomel should never be prescribed with iodid; it is also incompatible with organic substances. It is contraindicated in nephritis.

The theoretical objections to the use of so powerful a renal irritant as mercury in nephritis, was early emphasized, especially by Cohn, 1887, and supported by some clinical observations. It was claimed that there is a very marked tendency to mercurial symptoms, and that the nephritis is often made worse. The greater number of observers, however, hold the opposite view, viz., that calomel does not render the nephritis worse, whether it has a diuretic action or not. This is defended by Jendrássik, and by Heuck, 1889. Schild, 1892, reports 3 cases, in which he claims that a diuretic effect was obtained, together with a lessened per cent. of albumin; the daily output of proteid being unchanged.

Briefly, it seems certain that the doses of calomel which are advocated have never produced albuminuria in normal individuals, but the question of their effect on an existing nephritis is not sufficiently investigated to admit of a decisive answer. Great conservatism in its employment is therefore indicated.

The *mechanism of this calomel diuresis* is not understood, notwithstanding the investigations of Jendrássik, of Cohnstein, 1892, and of Vejux-Tyrode and Nelson, 1903.

Metallic Astringents.—

(A) Members.—Of the *metallic salts* the most actively astringent is lead acetate; but this cannot be used internally, nor for any length of time externally, on account of the danger of chronic poisoning. Next in activity comes alum, and especially the burnt alum (alum which has been roasted, so as to deprive it of its water of crystallization, and which therefore acts not only as a metallic astringent, but mechanically by withdrawing water). Next to alum, come the soluble zinc salts, the sulphate, the acetate, and the sulphocarbolate. Then, after these, insoluble zinc salts, oxid and carbonate. Of other insoluble metallic salts the subnitrate of bismuth and the oxalate of cerium are most commonly used. Then come the caustic salts in proper dilution. The most important is silver nitrate. Then the iron salts in dilute solution; iron sulphate, about 5%; ferric chlorid, about 3%.

In actual use, these different astringents are frequently combined. Whether this has any advantage is somewhat difficult to say. Better results could perhaps be secured by using only one astringent, since its action could be much more exactly controlled.

(B) The **therapeutic value** of astringents consists in lessening of the phenomena of chronic inflammation, especially catarrh of mucous membranes. Since their own action is primarily an irritant one, they are apt to increase acute inflammations, and are not so well adapted to their treatment.

The manner of action, and the general indications of astringents are discussed on page 665; the styptic action, on page 510.

For use on open *wounds, ulcers, abscesses,* etc., for the astringency and a mild nutritive stimulation leading to repair, silver nitrate is the most useful. Next to this, the soluble zinc salts; then alum. They are used in strengths of from ½% to 5%. The insoluble astringents may be used as dusting-powders, or in the form of ointments — 5% to 20%. It must not be forgotten that absorption is fairly free from open surfaces, and calomel, bismuth, lead, etc., must be used with caution. Zinc oxid is quite safe, and is one of the most useful.

The *mucous membranes* which are easily accessible to the local action of astringents are those of the mouth, conjunctiva, nose, genito-urinary tract, and rectum. The same salts as in the case of open wounds can be used, as also tannin. They are employed in somewhat weaker solution, as gargles, washes or injections. The usual strength is from ½ to 1%. For vagina or rectum, double this; in the conjunctiva and nose, perhaps one-fourth of this. The strength, as with all local medication, must be adjusted to the anatomic peculiarities of the surface: It should be very different for the cornea and for the plantar surface of the foot. In the case of the genito-urinary tract, irritation is particularly undesirable. For this reason non-irritant proteid compounds of silver have become popular within recent years — Nargol, Protargol, Argentamin.

Astringents cause actual constriction of the mucous membranes, and may in this way bring about the complete disappearance of small polypi.

In the *alimentary canal* the astringents are useful mainly in lessening the reflexes resulting from inflammation; *i. e.,* the vomiting and diarrhea.

Against *vomiting,* especially when caused by ulceration, the insoluble metallic astringents, especially the bismuth subnitrate and the oxalate of cerium, seem to be the most useful. These act not only in virtue of their astringency, but also somewhat after the manner of inert dusting-powder, affording an artificial protective covering to the walls of the viscus by adhering to them. Silver nitrate is also sometimes used in doses of about 1 centigram (⅙ grain), dissolved in water and given three times a day.

Their action on *diarrhea* is entirely similar. Bismuth is again preferred; silver nitrate is often very useful in the summer diarrhea of infants.

Vegetable Astringents (Tannins).—

These act precisely like the metallic astringents; they are somewhat less irritating and less stimulating. They are used principally against diarrhea; their employment dates back at least to the fourth century B. C.

The nature of these tannins has already been discussed on page 21. Whilst they all belong to the aromatic series and present certain chemic characters in common, their similarity is mainly a pharmacologic one, resting on the astringent action. This is connected with a remarkable property of precipitating very many classes of substances — proteids, connective tissue, gelatin, as also many alkaloids and glucosids.

There are, however, minor differences between different tannins, in the firmness and solubility of the eschars which they form. These differences may eventually prove of great therapeutic importance, but have at present been too little worked out to be utilized.

The tannins are *absorbed* to but a very small amount, which is excreted by the urine. The major part is decomposed before absorption, with the formation of a series of decomposition products, amongst which gallic and pyrogallic acids are especially prominent. Neither of these is astringent, so that the specific action of tannin is a *purely local* one. Even the trifle of tannin which escapes decomposition exists in the blood as the non-astringent sodium salt.

The effect of the *continued administration* of small amounts of tanninis has considerable importance, because they are contained in a number of beverages; as tea and certain wines. A mild astringent action may be tonic and beneficial; but larger quantities prove actually irritant, and may lead to gastro-enteritis.

Even small amounts of tannin interfere somewhat with absorption. This is largely due to their precipitating proteids. But these combinations are again decomposed in the alkaline intestine, so that the interference is not large.

In the actual experiments of Biberfeld (1903) on the absorption of normal saline solution from a Vella fistula, this was accelerated by 0.01% of tannin; 0.04% had no effect; 0.1 to 1% delayed absorption.

On the whole, one may say that the small quantities of tannin ordinarily taken with the food and drink are not injurious; but that large quantities (excessive tea drinking) are certainly deleterious. The tannin of coffee is scarcely astringent, and therefore lacks this action.

Therapeutic Employment.— The *ordinary tannin* (obtained from nutgall) can be used, in solution, on catarrhal mucous membranes, but is too irritant to be applied to open wounds. Its disagreeable taste and the gastric irritation which it produces in effective doses also preclude its internal administration in **diarrhea.** To be useful in this condition it must be prevented from acting until it reaches the intestine, where it should produce its effects slowly. These requirements are fairly well met by the *galenic preparations* of drugs containing tannin; the gums and resins which accompany it in these drugs serving to delay its action. These preparations (especially the Tinctures of Gambir, Kino and Krameria, in doses of 2 to 5 c.c. (½ to 1 teaspoonful) are very efficient.

Artificial Tannin Compounds.— The same object may be attained still better by employing certain artificial tannin compounds, which are insoluble in water and dilute acids, but soluble in dilute alkalies. These can be obtained by combining tannin with proteids (*Tannalbin* is an exsiccated tannin-albumen precipitate; *Tanocol* is a corresponding gelatin precipitate); with hexamethylenetetramin (*Tannopin*); or by transforming it into acetyl-tannin (*Tannigen*). All these products are incompatible with alkalin. They are yellowish, odorless and tasteless powders. *Dose,* 1 to 5 Gm. (15 to 75 grains); for children, 0.3 to 1 Gm. (5 to 15 grains).

Tannopin, and tannin-formaldehyde (*Tannoform*) can also be used as astringent dusting powders, for wounds and in hyperidrosis.

The insolubility of tannin compounds has been utilized in securing a more *prolonged local action of the kations.* It will be remembered that this is one reason for the more lasting local effects of galenics as compared with alkaloids. It has been suggested to prepare such combinations artificially, but these have not yet received an extensive trial.

MATERIA MEDICA OF TANNINS.

Acidum Tannicum (U. S. P., B. P.).— (*Tannin, Gallotannic Acid, Digallic Acid.*)— $HC_{14}H_9O_9$. Prepared from nutgalls. Soluble in 0.34 part water, 1 part glycerin, 0.23 part alcohol. Almost insoluble in ether or chloroform. *Dose:* 0.06 to 1.2 Gm. (1 to 20 grains) (0.5 Gm. = 7½ grs. U. S. P.).[1]

Preparations:

- *Collodium Stypticum* (U. S. P.).— (20%.)
- *Trochisci Acidi Tannici.*—U. S. P., each 0.06 Gm. (= 1 grain) Tannin; B. P., each 0.03 Gm. (= ½ grain) Tannin.
- *Unguentum Acidi Tannici* (U. S. P.).— 20% in Benz. Lard.
- *Glyceritum Acidi Tannica* (U. S. P., B. P.).— 20%.
- *Suppositoria Acidi Tannici* (B. P.).— Each 0.2 Gm. (3 grains) of Tannin.

The *tannin compounds* are discussed sufficiently in the text.

Acidum Gallicum (U. S. P., B. P.).— Gallic Acid.— $C_2H_2(OH)_3CO_2H + H_2O$.
Occurs in many plants, usually with tannic acid. Prepared by boiling tannin with dilute acids. It does *not* precipitate alkaloids, albumin, or glue. Sol. in 83.7 water, 4.14 alc., 12 glyc. *Dose:* 0.1 to 1.0 Gm. (2 to 15 grains) (1 Gm. = 15 grs., U. S. P.). Externally as astringent (1%), but acts weaker than tannin.

Crude Drugs Containing Tannin.— These are very numerous, and many might well be dispensed with. It will suffice for the student to emember the following preparations: Tinct. Gambir Comp.; Tinct. Krameriæ; Tinct. Kino; Ext. Hæmatoxyli.

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[1] Old solutions cease to precipitate glues, although they still color iron. Study Materia Medica Lesson 7.

The following list is arranged alphabetically. (Only the average (U. S. P.) doses are given.)

Catechu (B. P.).—Cutch—Extract of leaves and shoots of *Uncaria Gambier*. India. 45% catechu tannin.

Tinctura (½ to 1 ʒ); *Trochiscus* (1 gr.); *Pulv. Catechu Co.* (10 to 40 grs).

In the U. S. P. Catechu has been replaced by Gambir.

* *Coto.*—Bark of unknown plant. Bolivia. Cotoin, resin. *Dose:* 0.06 to 0.6 Gm. (1 to 10 grs.).

Cotoin.—Glucosid, said to be specific in cholera! also to check night-sweats in phthisis. 0.06 to 0.12 Gm. (1 to 2 grs.).

Eucalypti Gummi (B. P.).—*Red Gum.*—Gum from Eucalyptus species, Myrtaceæ. Australia. Kinotannic Acid, Catechin, and Pyrocatechin. *Trochiscus* (1 gr.).

Galla (U. S. P., B. P.).—*Nutgall.*—Excrescence on leaves of the oak Quercus infectoria, caused by the wasp Cynips tinctoria. Levant. 50 to 60% tannin, 2 to 5% gallic acid. 0.5 Gm. = 7½ grs.

Tinctura (U. S. P.).—20%. 4 c. c. = 1ʒ.

Unguentum (U. S. P., B. P.).—20%.

Ung Gallæ cum Opio (B. P.).—7½% opium.

Gambir (U. S. P.).—Extract prepared from leaves and twigs of *Ourouparia Gambir* (Rubiaceæ). Catechu-tannic acid (33 to 47%), catechin, etc. 1 Gm. = 15 grs. *Takes the place of Catechu.*

Tinctura Gambir Comp. (U. S. P.).—5% Gambir, 2% Cinnamon. 4 c. c. = 1ʒ.

Trochisci Gambir (U. S. P.).—0.06 Gm. = 1 gr.

Geranium (U. S. P.) — *Cranesbill.* — Rhizome of *G. maculatum* (Geraniaceæ). N. America. 12 to 17% tannin.

Fluidextr. Geran. (U. S. P.).—1 c. c. = 15 ♏.

Hæmatoxylon (U. S. P.) [*Hæmatoxyli Lignum,* B. P.].—Logwood. Heartwood of *H. campechianum,* Leguminosæ. Central America. 12% Hæmatoxylin.

Extr. Hæmatoxyli (U. S. P.).—Watery decoction, evaporated to dryness. 1 Gm. = 15 grs.

Hamamelidis Folia (U. S. P., B. P.).—Witchhazel.—Leaves of *Hamamelis virginiana,* Hamamilidi, acese. N. America. Collected in autumn. 8% tannin (Straub, 1899).

Fldextr. Hamam. Foliorum (U. S. P., B. P.).—2 c. c. = 30 ♏.

Liquor, Tinctura, Unguentum (B. P.).

Hamamelidis Cortex (U. S. P.).—The bark and twigs. 2 Gm. = 30 grs.

Aqua Hamamelidis (U. S. P.).—Watery distillate, to which 15% of alcohol is added. Vulnerary. (No tannin.) 8 c. c. = 2ʒ.

Kino (U. S. P., B. P.).—Inspissated juice of *Pterocarpus Marsupium,* Leguminosæ. India. 75% Kinotannic acid.

Tinctura Kino (U. S. P., B. P.).—4 c. c. = 1ʒ.

Pulv. Kino Comp. (B. P.).—5% opium. 5 to 20 grs.

Krameria (U. S. P.) [*Krameriæ Radix,* B. P.].—Rhatany.—The root of *K. triandra* (Peruvian K.), *K. Ixina* (Savonilla K.), or *K. argentea* (Para or Brazilian K.), Krameriaceæ. S. America. 20% Krameria-tannic acid.

Extractum K. (U. S. P., B. P.).—Dried watery extract. 0.5 Gm. = 7½ grs.

Fluidextr. K. (U. S. P.).—1 c. c. = 15 ♏.

Tinct. K. (U. S. P., B. P.).—20%. 4 c. c. = 1ʒ.

* Not official.

Study Materia Medica Lesson 7.

Syrupus K. (U. S. P.).—45% of fldext. 4 c. c. = 1ʒ.
Liq. K. Concent. (B. P.).—½ to 1ʒ.
Infus. K. (B. P.).—½ to 1℥.
Trochisci K. (U. S. P., B. P.).—0.06 Gm. = 1 gr.
Trochisci K. et Cocainæ (B. P.).—1/20 gr. cocain.

Quercus (U. S. P.).—*White Oak.* Bark of *Qu. alba,* Cupiliferæ. N. America. 6 to 11% quercitannic acid. 1 Gm. = 15 grs.

Fluidextractum Quercus (U. S. P.).—1 c. c. = 15 ♏.

Rhus Glabra (U. S. P.).—*Sumach.*—Dried fruit. N. America. 6 to 27% tannic acid, malates. 1 Gm. = 15 grs.

Fluidextr. Rhois Glabræ (U. S. P.).—1 c. c. = 15 ♏.

Rubus (U. S. P.).—*Blackberry.*—Bark of rhizome of *R. villosus, nigrobaccus or cuneifolius,* Rosaceæ. N. America. 10 to 13% tannic acid.

Fluidextr. R. (U. S. P.).—1 c. c. = 15 ♏.
Syrupus R. (U. S. P.).—25% of fldext. 4 c. c. = 1ʒ.

The following plants, which are used in popular medicine, may be classed amongst the astringents, although many of them contain other principles:

Aegle Mamelos — Bael Fruit.
Carya — Hickory.
Castanea — Chestnut.
Cornus — Dogwood.
Corylus — Hazelnut.
Heuchera — Alum Weed.
Juglans — Walnut and Butternut.
Kalmia — Mountain Laurel.
Potentilla — Cinquefoil.
Rumex (especially crispus) — Yellow Dock.
Thea — Tea.
Vaccinia — Cranberry.
Viola — Pansy.

(C) SPECIAL USES OF ASTRINGENTS.

ANTIDIARRHŒICA:

i. e., Medicines used to lessen peristalsis. The indications for these are to check diarrhea, in peritonitis, and after abdominal operations.

Diarrhea is due to *inflammatory irritation,* the result of faulty digestion, drugs, or bacteria (except in the case of a few *poisons* which stimulate the nerves or muscles directly).

The *etiology* therefore indicates *treatment* by: (1) Removal of the irritant agent, by purging. (2) Limitation of the production of the irritant agent by antiseptics and by reduction of diet (to starchy food). (3) Neutralization of the agent (in cases of acid formation, by alkalies): Chalk, Calcium phosphate, Lime-water. Charcoal is often very efficient.

The *peristalsis* itself may be *diminished* by:

1. Heat, in the form of hot drinks or hot applications to the abdomen.
2. Astringents.
3. Drugs acting upon nerves: Opium or Belladonna.

The diarrhea often results in considerable *weakening* of the patient, to be counteracted by reflex stimulants, as camphor, alcohols, etc.

The principal *Astringents* which are useful in this connection are:

Vegetable:		Mineral:	
Gambir	Rhatany	Bismuth subnitrate	Aluminum hydrate (1 Gm.).
Kino	Tea	" subgallate	———
Hæmatoxylon	Claret	Zinc Oxid, 0.1	Alum enema, 1%.
Coto	Tannin	Silver Nitrate (Pills), 0.01	

These are frequently usefully combined, as in the:

Mistura Contra Diarrhœam (N.F.).—(Sun Cholera Mixture.)—Equal

parts of Tincture of Opium, Capsicum, Rhubarb, Camphor, Peppermint. *Dose,* to one teaspoonful. Or: Tr. Opium, Tr. Catechu, Tr. Rhubarb, Sp. Peppermint, Bismuth subnitrate, etc.

ASTRINGENT STYPICS.

All the metallic salts, the irritant as well as the astringent, and also the vegetable astringents, act as local **styptics;** *i. e.,* lessen local hemorrhage. They do so mainly by the formation of precipitates which occlude the lumen of the small vessels, just as it is occluded ordinarily by fibrin. (Whilst the majority lessen the formation of fibrin, this is offset by the precipitation.) Besides this precipitation, they also act by injuring the vessel walls in such a way as to produce thrombosis. This is claimed especially for zinc chlorid.

It is scarcely needful to mention that astringents will act only at the place to which they are applied. It is necessary that they come into actual contact with the bleeding vessels. They cannot act through a large clot of blood, and if such exists, it must first be removed. At one time they were used internally with the idea of producing astringent action in remote places; iron was given by the mouth to check bleeding in the uterus. This was entirely irrational. Their action cannot even extend beyond the stomach, since they are precipitated or decomposed in the intestine.

The indications for the use of styptics are to lessen bleeding, especially capillary oozing. They are sometimes injected into hemorrhoids, and have even been injected into aneurysms. Their injection into larger vessels is dangerous, as it may produce embolism.

The most useful of the metallic styptics are the iron salts, especially the ferric chlorid and ferric sulphate. The ferric chlorid is used either as the solution, or tincture, quite largely diluted with water. Cotton may be steeped in this, forming "styptic cotton."[1] Next comes alum, especially the burnt alum. Then the tannins in any form.

Besides these, any substance which gives a precipitate with proteids will act as a styptic in the same manner; *e. g.,* dilute acids in concentrations which need not be at all caustic (vinegar and lemon juice). Quite a number of purely mechanical measures favor the formation of clot; for instance, ordinary cotton or Pengawhar Djambe (this also contains tannin). Cobwebs also form a popular and very effective measure for producing the same result, but are unfortunately very septic. One may obtain the same effect by fine powders which have a strong attraction for water. In case of emergency powdered or granulated sugar is a good styptic, and at the same time antiseptic. Other styptic measures are position, raising the limb and keeping it quiet so as to reduce the local congestion; local pressure; depression of the vasomotor center by narcotics; direct constriction of the vessels by the application of cold, or by drugs, such as cocain, suprarenal extract, hydrastinin, etc.

Sweating Feet: Besides hygienic treatment, the conditions are met by:

1. Acids (see p. 677).
2. Astringents: Silver nitrate 10%, painted on repeatedly until the skin is partly destroyed. Other astringents, 1 to 5% solution, Tannoform.
3. Antiseptics: Boric acid (saturated solution).
Potass. Permanganate (1:1000).
Salicylic acid 10:90 Talcum or Zinc Oxid.

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[1] *Ferripyrin,* a ferric chlorid-antipyrin compound, is claimed to be less irritant. It is used as 10 to 20% solution in water.

TABLE XIV. STRENGTH OF MOST USEFUL SOLUTIONS OF ASTRINGENTS AND ANTISEPTICS.[1]

	Touching Ulcers, Gargles, Rectal and Vaginal Injections.	Urethral Injections and Eye-washes.	Baths (Gm. per Bath, 200 Liters — 30 Gal.).
Neutral Salts:			
Sodii Chloridum	1%	0.9%	4 Kg.
Alkalies:			
Sodii Bicarbon.			
Sodii Carbonas.	0.2 to 1%	0.2%	100 Gm.
Potassii Carbonas			100 Gm. 100 Gm.
Sulphids:			
Pot. sulphurat..			50 to 150 Gm.
Acids (Mineral)	0.5%	0.5%	30 c.c. (1 oz.)
Haloids:			
Iodin	0.1 to 1%		
Metallic Salts:			
Zinc Sulphate or Phenolsulphonate	1.5 to 1%	0.2 to 0.4%	
Mercuric Chlorid	0.05 to 0.1%	0.025%	
Liq. Plumbi Subacet. Dil.	Full strength.	Full strength.	
Silver nitrate..	0.5 to 5%	0.2 to 0.5%	
Tr. Ferri Chloridi	10% (of Tr.)		
Alumen and Alum. Salts..	1 to 3%	0.25%	
Cupric Sulphate	1%	0.5%	
Lead Acetate..	1%	0.5%	
Tannins:			
Tannic Acid...	1 to 3%	0.5 to 2%	
Miscellaneous:			
Boric Acid, or Borax	4% (sat'd)	2% (½ sat'd)	
H_2O_2	¼ to ½ of Aqua.	⅛ of Aqua.	
Pot. Permangan.	1 to 2%	0.4%	
Glycerin	20%	10%	
Phenol	1%	0.2%	
Thymol, Essential Oils.....	Saturated. Watery.	Saturated. Watery.	
Alkaloids:			
Morphin		0.2%	
Hydrastinin ...		0.1%	
Most Alkaloids for Eye		0.5 to 1%	

Baths: Usually taken in the evening before going to bed. Metal-lined tubs must be avoided for medicated baths.

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[1] (1% = 5 grains per ounce.) When several are combined, the dose of each must be correspondingly decreased.

Gargles: No toxic substance should be used, especially with children, on account of the danger of swallowing. The metallic salts attack the teeth, so that they cannot be employed for a long time.

Urethral Injections: Always have the patient urinate just before injecting, to remove bacteria. Let injection remain at least one minute, then let flow out, but patient should not micturate immediately after.

THERAPEUTICS OF CAUTERIZATION.

Cauterization — the destruction of tissue — is sometimes employed for severe *counter-irritation*, but particularly to *remove tissue:* (1) In cases of poisoning, snake-bite, etc.; (2) for the removal of pathologic tissues, tumors, warts, etc.; (3) indolent granulations, etc.; (4) to cause cicatricial contraction of hypertrophied mucous membranes (nose, etc.); (5) for removing the nerves of teeth; and (6) to remove superfluous hair.

In very many cases the chemic cautery has been replaced by galvano- and thermocautery, which are more prompt and permit a more exact limitation of the cauterized area. On the other hand, the slower effect of chemic caustics is of advantage in permitting a graduation in the strength of the action, or in confining it to certain tissue elements. Pathologic formations, being less staple, are in this way more profoundly altered than normal tissue.

The caustics may be applied in solid form (sticks, or fused at the end of a probe), in paste, or in solution — the first being the most strictly localizable, the last the most diffuse. In the latter case, or when the eschar liquefies, the surrounding tissue should be protected by court-plaster.

TABLE OF MOST IMPORTANT CHEMIC CAUTERIZANTS, AND THEIR USES.[1]

Acidum Nitricum: On glass rod. Warts and local tubercles.
Acidum Chromicum: Fused on probe (4).
Acidum Lacticum: On Cotton. Tuberculous tissue.
Acidum Trichloraceticum: On Cotton (2). Warts.
Acidum Carbolicum: Destruction of infected tissues.
Potassa: Stick.
Calx: Paste (6).
Potassa cum Calce: Paste.
Soda: Stick.
Argenti Nitras: Stick (4, 3).
Zinci Chloridum: Solution (3).
Cupri Sulphas: Crystal. Ulcers of conjunctiva, larynx, etc.
Hydrargyri Bichloridum }
Liquor Hydrargyri Nitratis } Luetic tissue.
Acidum Arsenosum: Dental nerve. (2.5 mg.— $^1/_{25}$ grain — in cavity, guarded by cotton.)

Study Materia Medica Lesson 8.

[1] Numbers refer to indications in preceding paragraph.

CHAPTER XXIX.

IRRITANTS (Continued).—ORGANIC AND PHYSICAL IRRITANTS.

Any substance which is volatile will penetrate cells in virtue of this property. Not being a normal constituent of protoplasm, it will act as a "molecular foreign body," and cause irritation, just as gross foreign bodies cause irritation when introduced into the organism. Their action may therefore be looked upon as physical, and as connected with their volatility.

Many volatile irritants have already been studied, and it is only necessary to review them by name. Their main action is the same as that which will be studied more in detail below.

Volatile Irritants:

1. *Fatty Series:* Alcohol, Ether, Chloroform, Petroleum, etc.
2. *Aromatic Series:* Benzol, Phenol, the Aromatic Acids, etc.
3. *Volatile Acids* (Acetic, Formic, etc.) and *Volatile Alkalies* (Ammonia).
4. *"Organic Volatile Irritants."*

The *organic volatile irritants* may be divided into two groups:

1. Those acting *only in virtue of their volatility*—represented by Turpentine.
2. Those having a *specific action*—represented by Mustard.

VOLATILE OILS (TURPENTINE GROUP).

Introduction.—This group comprises the majority of volatile oils (see page 23) and their stereoptenes, and may also be made to include the balms and resins which contain volatile oils.

These oils belong chemically to the aromatic series, and resemble the phenols and camphor in their systemic actions. They are also rather weakly *antiseptic.* As they are commonly used, the local actions alone come into play. Since they do not unite chemically with protoplasm, whilst they penetrate quickly and deeply in virtue of their volatility, they combine a maximum of sensory irritation with a minimum of tissue destruction—the latter can only occur in the severest grades of action, as inflammatory necrosis. They are therefore especially useful for *counter-irritation.* The sensory stimulation is followed by *local anesthesia.* The stimulation of certain sensory nerves is somewhat specific: most of the volatile oils have peculiar, characteristic odors, which determines their use as *flavors* (see Chap. VI B). Menthol stimulates the *cold-nerves* in a peculiar manner. After their absorption, they irritate the kidneys, and produce *diuresis*. The volatile oils differ sufficiently in the details of their local actions to make a therapeutic grouping desirable. It should be remembered, however, that the differences are merely quantitative.

The value of essential oils (particularly those enumerated as urinary antiseptics) in **chronic inflammations** of all sorts has been abundantly proved by clinical observations and laboratory experiments. They are much less useful in acute inflammatory conditions. Their action is partly explained by their aseptic and irritant qualities. But the fact that they also lessen aseptic inflammations at points remote from the site of their application, *i. e.*, through the blood, shows that there is somewhat specific in their action. They effect this result by lessening the formation of exsudates and by hastening their absorption. The explanation probably lies in a chemotaxis, an attraction for leucocytes. In this way they withdraw these cells from the inflamed area into the blood. (Winternitz, 1901).

Systemic Actions of Volatile Oils.— The principal central effects of volatile oils are reflex. With the ordinary doses, no direct action whatever can be observed. When they are injected intravenously, however, they act on the nervous centers, especially the brain and medulla. These are first stimulated, then depressed. The details have been but imperfectly worked out, and have little practical importance. The degree of stimulation varies for the different oils. Turpentine has scarcely any effect, whilst absinthe produces violent epileptic convulsions, mainly of cerebral origin. The depression is more uniform: The majority (valerian, fennel, chamomile, eucalyptus, mint, rosemary, turpentine) diminish the reflex excitability, so that large doses will entirely prevent strychnin convulsions in rabbits. The effective doses are, however, entirely too large to make it possible to employ this action in man.

According to d'Ormea (1903), the intravenous injection of volatile oils causes a peculiar dilation of the *cerebral vessels*, the volume of the brain increases, whilst the pressure in the circle of Willis falls. This effect is strongest with absinthe, weak with anise or lemon. Camphor has a similar effect. The general blood-pressure also falls in most cases, but quite independently of the changes in the cerebral circulation.

If volatile oils are injected **hypodermically**, they produce at first the reflex action, and in a more marked degree than when they are applied to the surface of the skin. Later their systemic, and still later the renal, actions take place.

Olfactory Stimulants.

Odorous substances produce pronounced reflex effects. Pungent and aromatic drugs cause in this way a prompt medullary stimulation, increasing the respiration and blood-pressure, and slowing the pulse. They are especially useful in fainting. They are employed by inhalation. * *Acetum Aromaticum* (N.F.), * *Tinctura Aromatica* (N.F.) and *Tinctura Lavandulæ Composita* (U.S.P., B.P.) are useful mixtures for this purpose. (They are also employed for *sponging* the skin in fever, producing a grateful refrigeration.) The inhalation of other volatile substances may be substituted, such as ammonium carbonate (in the form of smelling-salt), ether (as Spiritus Aetheris), etc.

Any pungent substance will answer in an emergency; the burning of a feather under the nose of the patient is a standard household measure.

Substances which produce sneezing (**sternutatoria** or *errhines*) act in a similar manner, but have rather passed out of fashion. They are sometimes also useful as local counterirritants in nasal catarrh.

Amongst these may be mentioned:

Tobacco Snuff.
Veratrin 1:1000 Starch.
Ipecac.
Soap-bark or other Saponins
Pepper.
Euphorbium, etc.

Hysteric Sedatives.

Asafetida, valerian, and some other allied drugs, have been found empirically to possess a remarkable sedative effect in hysteria. The existence of this action can scarcely be doubted, although it cannot be explained. *Valerian,* which has been investigated most thoroughly (Pouchet and Chevalier, Kionka, 1904) causes the usual effects of volatile oils, when it is injected; in small doses, psychic exaltation and rise of blood pressure form cardiac and vasomotor stimulation; in larger doses, central sensory and motor depression. It is very doubtful, however, whether these systemic effects can be elicited by the ordinary doses. It appears more probable that the therapeutic action is due to olfactory reflexes. It is at least remarkable that all the drugs which produce these effects are malodorous to most normal individuals; and it is stated that they are often rather grateful in hysteria.

MATERIA MEDICA OF ANTIHYSTERICS.

Valeriana (U.S.P.) [*Valerianæ Radix,* (B.P.)].—Valerian.—Rhizome and roots of Valeriana officinalis; Valerianceæ. Europe and Northern Asia; cultivated.

Constituents: ½ to 2% volatile oil. Valerianic and other organic acids; Tannin and Resins.

The oil consists of esters of valerianic acid, especially with borneol. These are the bearers of the action; free valerianic acid and its salts being quite ineffective. The fresh root is also ineffective, the esters being formed only during drying, by the action of oxidases (Kochmann, 1904). The juice of the fresh plant also produces different effects from the dried valerian (Pouchet and Chevalier, 1905). The esters again deteriorate by oxidation on keeping. Kionka (1902) has recommended the artificial *diethylamid ester* of valerianic acid as a relatively stable substitute.

Preparations:

Fluidextr. Valerianæ (U.S.P.).—Three-fourths alcohol. 2 c.c. = 30 ♏.

Tinct. Valer. (U.S.P.).—20%. 4 c.c. = 1 ʒ.

Tinct. Valerianæ Ammoniata (U.S.P.).—20%, with Arom. Sp. Ammon. 2 cc. = 30 ♏ (diluted).

Tinct. Val. Ammon. (B.P.).—½ to 1 ʒ.

* *Valyl* (Diethylamid of valerianic acid), a colorless liquid of peculiar odor and burning taste; is marketed as capsules containing 0.125 Gm. (2 grains). It is recommended as a substitute for valerianic acid, one to three capsules being the dose.

Valerates (*Valerianates*): Of very little value. Given in *doses* of 0.06 to 1 Gm. (1 to 15 grs.), generally in capsules. They are colorless crystals of a valerianic odor.

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* Not official.

Study Materia Medica Lesson 9.

Ammonii Valeras (U.S.P.).— $NH_4C_5H_9O_2$.— Very sol. in water or alc. 0.5 Gm. = 7½ grs.

Zinci Valeras (U.S.P., B.P.).— $Zn(C_5H_9O_2)_2 + 2H_2O$. Sol. in 50 water, 35 alc. 0.125 Gm. = 2 grs.

* *Ac. Valerianicum.*— $HC_5H_9O_2$. Sol. in 30 water, readily in alc.

Asafœtida (U.S.P.) [*Asafetida*, B.P.].— A gum-resin from the root of Ferula fœtida, Umbelliferæ. Turkestan and Afghanistan. (Also used as carminative.) 0.25 Gm. = 4 grs.

Constituents: 3 to 9% Volatile oil; 20 to 30% Gum; 45 to 70% Resin. (The alcoholic preparations yield turbid mixtures with aqueous liquids.)

Preparations:

U.S.P.:

Tinctura.— 20%. 1 c.c. = 15 ♏.

Emulsum.— 4%. 16 c.c. = 4 ʒ. (*Milk of Asafetida, Asafetida Mixture.*)

Pil.— Each = 0.2 Gm. = 3 grs. *Dose:* Two.

B.P.:

Tinct., ½ to 1ʒ; *Pil. Aloes et Asaf.*, 4 to 8 grs.; *Pil. Galbani Comp.*, 4 to 8 grs.; *Spir. Ammoniæ Fetidus*, 20 to 40 ♏.

Sumbul.— *Musk-Root.*— Rhizome and root of undetermined plant (generally supposed to be *Ferula Sumbul*, Umbelliferæ, Central Asia). 2 Gm. = 30 grs.

Constituents: Volatile Oil, Resins, Valerianic and other acids.

Extractum Sumbul (U.S.P.).— Fluid ext. evaporated to pilular consistence. 0.25 Gm. = 4 grs.

Fluidextractum Sumbul (U.S.P.).— Three-fourths alcohol. 2 c.c. = 30 ♏.

Tinctura Sumbul (B.P.).— 10%. Two-thirds alcohol. *Dose:* 4 to 15 c.c. (1 to 4 drachms).

Moschus (U.S.P., B.P.).— Musk (see p. 108). This substance is ordinarily employed as an ingredient of perfumes. Its physiologic action has been but little studied. It has been recommended in hysteria, and had at one time considerable reputation as a restorative in collapse (5 c.c. of the tincture). It has fallen into disrepute.

* **Symplocarpus.**—(*Skunk-cabbage.*) Root of Symplocarpus fœtidus, Armideæ. North America. *Dose:* 0.3 to 1 Gm.

* **Cataria.**—(*Catnip.*) The herb of the Nepeta Cataria, Labiatæ. North America. Volatile oil. *Dose:* 1 to 4 Gm. (¼ to 1 drachm) as infusion. The odor of the herb produces remarkable excitement in cats.

Oleum Erigerontis (U.S.P.).— The volatile oil from the herb Erigeron Canadense (fleabane); Compositæ. North America. *Dose:* 1 c.c. = 15 ♏.

Volatile Oils Used Mainly for Counterirritation.

When applied to the skin, the irritant action of these oils is mainly sensory and vascular, progressing only to rubefaction. They form valuable ingredients of liniments for inflammatory swellings (hence vulneraries) and muscular pains (Witchhazel, Arnica); for chronic rheumatism (Turpentine); etc.

Materia Medica of Rubefacient Oils.

Administration.— As rubefacients, the oils are diluted with 3 to 10 volumes of alcohol or a fatty oil. Their *dose* internally is 0.05 to 0.3 c.c. (1 to 5 minims). They are incompatible with water.

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* **Not official.**

Oleum Terebinthinæ (U.S.P., B.P.).—(*Spirits of Turpentine.*) A volatile oil (a mixture of several isomeric hydrocarbons of the formula $C_{10}H_{16}$) obtained by distillation from Turpentine.[1]

Turpentine Oil is insoluble in water, soluble in 3 volumes of alcohol, and in all proportions of oils.

It is employed *externally* in liniments.

It is used as a *spray and in vapor* in bronchitis (teaspoonful to tablespoonful for pint of hot water). Stupes and Enemata are useful in the *meteorism* of typhoid fever.

It is also sometimes taken internally against respiratory and urinary diseases, but had best be replaced by Terpene. It gives to the urine an odor resembling violets.

As *Anthelmintic* it is given in doses of 2 to 15 c.c. (½ to 4 drachms).

Oil of Turpentine undergoes slow changes on exposure to the air, becoming *ozonized*. This is used as an antidote in phosphorus-poisoning (see p. 657).

Preparations:

Oleum Terebinthinæ Rectificatum (U.S.P.).— Prepared by redistilling the oil over soda to remove the odorous abietic acid. *Dose:* 1 c.c. = 15 ♏.

Linimentum Terebinthinæ (U.S.P.).— One part Oil of Turpentine, two of Resin Cerate. (B.P., contains Camphor.)

Linimentum Terebinthinæ Aceticum (B.P.).— Contains Camphor and Acetic Acid.

Emulsum Olei Terebinthinæ (U.S.P.).— 15%.

* *Petroleum* (*Coal Oil*) resembles oil of turpentine in its local actions (see Index).

* *Oleum Succini* (Oil of Amber) is obtained by the distillation of amber (a fossil resin). The crude oil is dark brown, but it can be obtained colorless by rectification.

Oleum Lavandulæ (U.S.P., B.P.); from the fresh flowers of lavender (see Index).

Oleum Cajuputi (U.S.P.).— From leaves of *Melaleuca Leucadendron,* Myrtaceæ; East Indian Islands.

Oleum Rosmarini (U.S.P., B.P.).— From leaves of *Rosmarinus officinalis,* Labiatæ; cultivated in temperate zone.

Arnica (U.S.P.).— Flowers of *Arnica montana,* Compositæ; Europe. Contains a volatile oil, small quantities of volatile acids, and an acrid bitter principle. Used externally as

Tinctura Arnicæ Florum (U.S.P.).— 20%. One-half alcohol. 1 c.c. = 15 ♏.

Arnicæ Radix (B.P.) is similar to the flowers in composition and action.

Tinctura Arnicæ (B.P.).— 5% in three-fourths alcohol.

Aqua Hamamelidis (U.S.P.). [*Liquor Hamamelidis,* B.P.].—(Witch-hazel Water, Witch-hazel Extract.) Made by distilling the fresh twigs of *Hamamelis Virginiana* (see Index).

Pix liquida and Ol. Erigeron. (see Index) are also used as rubefacients.

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[1] The name "turpentine" is popularly applied to the Oleum Terebinthinæ. It refers more properly to:

Terebinthina (U. S. P.) [*Thus Americanum* (B. P.)], *Turpentine* is a solid oleoresin, obtained from various pines (Pinus, Coniferæ; United States and other countries).

The solid *American or Virginian Turpentine* is obtained mainly from Pinus palustris. *Canada Balsam* (Terebinthina Canadensis, U. S. P., from Abies balsamea) and *Venice Turpentine* (from Larix decidua) are thick and adhesive oils.

Rosin (Resina, U. S. P., Colophonium) is the solid resin which remains after the oil has been distilled from the turpentine.

* Not official.

Materia Medica Lesson 9.

Volatile Oils, etc., Used Mainly for Stimulation of Ulcers and Open Wounds.

These comprise the balsams — mixtures of resins, volatile oils, and aromatic (antiseptic) acids. They are viscous to solid, and are employed as alcoholic solutions. The evaporation leaves a protective and stimulant coating of the balsam.

Balsamum Peruvianum (U.S.P., B.P.).— A thick balsam, obtained from *Toluifera Pereiræ,* Leguminosæ; Central America. Sol. in alc. *Dose:* internally, 1 Gm. = 15 grs.; externally, on lint.

Myrrha (U.S.P., B.P.).— A solid gum-resin obtained from *Commiphora Myrrha,* Burseraceæ; Africa and Arabia. 0.5 Gm. = 7½ grs.

Tinctura Myrrhæ (U.S.P., B.P.).— 20% in alcohol. Externally, diluted with 5 to 10 volumes of water. Internally, 1 c.c. = 15 ♏.

Myrrh is also a carminative.

Styrax (U.S.P., B.P.).— A thick balsam obtained from *Liquidambar orientalis,* Hamamelaceceæ; Asia Minor. *Dose:* 1 Gm. = 15 grs.

Benzoinum (U.S.P., B.P.).—A solid balsam obtained from *Styrax Benzoin,* Styraceæ; Sumatra, etc. Volatile Oil, Benzoic and Cinnamic Acids.

Preparations:

Tinctura Benzoini (U.S.P.).— 20% in alcohol. 1 c.c. = 15 ♏.

Tinctura Benzoini Composita (U.S.P., B.P.).—(*Friar's Balsam, Turlington's Balsam.*) (Mainly used internally as carminative and purgative.) Contains Benzoin, Storax, Tolu, and Aloes. *Dose:* 2 c.c. = 30 ♏.

The original formula was more complicated. It may be found in the National Formulary as

* *Mistura Oleo-Balsamica* (N.F.).— An alcoholic solution of volatile oils and Balsam of Peru.

Other measures employed in the treatment of Ulcers.

The indications in the medical treatment of ulcers may be summarized as:

In all cases:
- 1. To stimulate normal growth and cell division.
- 2. To form a protective covering against the irritation of the air, etc.
- 3. To keep the surface aseptic.

In special cases:
- 4. To destroy unhealthy tissue.
- 5. To lessen pain.

Several objects may often be attained by the same drug. Almost every irritant produces secondarily anesthesia. Every irritant which coagulates protoplasm forms a protective covering. Almost every irritant is to some extent antiseptic. But according as one or the other action predominates, the most useful of these drugs may be classified as follows:

1. *Stimulating and forming a rather lasting pellicle of coagulated protoplasm;* mildly antiseptic:

(*a*) The soluble metallic salts, applied with a brush, in 2 to 5% solution; particularly $AgNO_3$ or $ZnSO_4$.

(*b*) The insoluble metallic salts — these also act as absorbents: Zinc oxid; bismuth subnitrate or subgallate; calomel. The last two should only be used on small surfaces. The calomel is also particularly antiseptic; it is usually diluted 5 to 10 times with ZnO. These may be used dry, or in the form of ointments.

2. *Stimulating, but pellicle not lasting:*

$ZnCl_2$, 1%
Alcohol, 20 to 50% } applied with brush.
Chloral, 2%

3. *Producing a lasting stimulation and a resinous protective covering.* Usually incorporated in dressing. Balsams (see above).

4. *Destroying tissue:* $AgNO_3$ stick; $CuSO_4$, 5%.

5. *Antiseptic:* Any of the usual antiseptics may be used for cleansing the surface. But if it is desired to keep it antiseptic, a powder-dressing should be used, such as Iodoform, Aristol, Boric Acid (impalpable powder), Calomel. These also act as absorbents.

Volatile Oils used mainly in Urethritis and Cystitis.

The action of these oils and resins is largely antiseptic; they seem to have a rather specific action on *gonococci;* for it has been shown that the urine from patients treated with copaiba is fatal to these bacteria, whilst it is still a good culture medium for other varieties. They seem to be superior for this purpose to other urinary antiseptics, such as urotropin, sodium salicylate or benzoate, or uva ursi. They are most useful in the later stages of the urethritis.

The drugs of this group are always used by mouth, not locally. They cause considerable *gastric irritation,* which may be lessened by giving them in capsules on a full stomach. It is claimed that the addition of pepsin is also useful in this connection.

The drugs are *excreted* in the urine for the most part in combination with glycuronic acid; the compounds retaining the antiseptic and irritant action. Since glycuronic acid reduces Fehling's solution, they may simulate glycosuria. Copaiba and sandalwood are precipitated from the urine by acids,[1] simulating albuminuria. The differentiation may be made by adding an excess of alcohol to the boiled urine: this dissolves the resins, but not the proteids.

Copaiba (U.S.P., B.P.) (Balsam of Copaiba).—A liquid natural oleoresin from *Copaiba Langsdorffii* and other species, Leguminosæ. Brazil and Venezuela.

Constituents: Volatile Oil, Resin, Copaivic Acid.

It is not known which of these is most concerned in the action; but it is very likely that they all contribute. For this reason there seems little ground for the following preparations. Copaiba is insoluble in water, but soluble in alcohol or oils. It has an unpleasant taste and odor, and is apt to irritate the stomach. It is therefore best given in capsules, or at least on a full stomach. The *dose* is 1 to 4 c.c. (¼ to 1 drachm). (1 c.c. = 15 ♏.)

It may be made into pills with Magnesia (*Massa Copaibæ,* 94%). *Dose,* as the last.

Preparations:

Oleum Copaibæ (U.S.P., B.P.).—The volatile oil distilled from copaiba. 0.5 c.c. = 8 ♏.

(Copaiba is not a true balsam, since it does not contain cinnamic or benzoic acid.)

A favorite method of using this drug in gonorrhea is in the form of—

* *Mistura Copaibæ Composita* (N.F.).—(*Lafayette Mixture.*) An emulsion containing as active ingredients ⅛ each of Copaiba and Sweet Spirits of Niter. *Dose:* 4 to 8 c.c.

Cubeba (U.S. P.) [*Cubebæ Fructus,* B.P.].—The unripe fruit of *Piper Cubeba,* Piperaceæ. Java; cultivated.

Contains a volatile oil and resin, the latter containing cubebic acid.

Whilst the oil is the most frequently employed, the oleoresin or fluid extract would be more rational, as the resin is probably also concerned in the action. Cubeb is less irritant than copaiba. The fluid preparations are made with alcohol, and are precipitated by water.

Study Materia Medica Lesson 10.

[1] Exercise 13.

Preparations:

Oleum Cubebæ (U.S.P., B.P.),
Oleoresina Cubebæ (U.S.P.),
0.3 to 1.2 c.c. (5 to 20 minims); may be given on sugar or in capsules. (0.5 c.c. = 8 ♏, U. S. P.)

The oleoresin is prepared by evaporating an alcoholic extract. If it shows a deposit, this should be rejected.

Fluidextractum Cubebæ (U.S.P.).— 1 c.c. = 15 ♏.

Tinctura Cubebæ (B.P.).— 20%. *Dose:* 2 to 12 c.c. (½ to 3 drachms).

Trochisci Cubebæ (U.S.P.).— Each contains 0.02 Gm. of the oleoresin. *Dose:* 1 to 6.

Oleum Santali (U.S.P., B.P.).— A volatile oil distilled from the wood of *Santalum album,* Santalaceæ. Southern India. *Dose:* 0.1 to 0.6 c.c. (2 to 10 minims). (0.5 c.c. = 8 ♏, U. S. P.)

Matico (U. S. P.).— The leaves of *Piper angustifolium,* Piperaceæ. Tropical America. Contain a volatile oil, resins, etc.

Preparations:

Fluidextractum Matico (U. S. P.).— Three-fourths alcohol; turbid with water. *Dose:* 2 to 8 c.c. (½ to 2 drachms). (4 c.c. = 1 ʒ, U. S. P.)

Volatile Oils Used Mainly as Diuretics.

All volatile oils irritate the kidneys in the course of their excretion. Therapeutic doses produce diuresis; whilst toxic doses cause nephritis, diminishing the urine and rendering it albuminous. These irritant diuretics should therefore not be used in acute nephritis and inflammation of the urinary passages. All the volatile oils have the diuretic action. The most commonly used are Juniper and Buchu. Terpene hydrate and cubeba are also employed for this purpose.

Juniperus (U.S.P.).—*Juniper Berries.*— The fruit of *Juniperus communis,* Coniferæ. Temperate zone. *Active constituent:* A volatile oil, isomeric with Oil of Turpentine.

Used as infusion, corresponding to 4 to 8 Gm.

Oleum Juniperi (U.S.P., B.P.).— The volatile oil distilled from the above. *Dose:* 0.1 to 0.6 c. c. (2 to 10 minims) (0.2 c. c. = 3 ♏, U.S.P.); usually given as one of the spirits:

Spiritus Juniperi (U.S.P., B.P.).— 5%. *Dose:* 2 to 4 c. c. (2 c. c. = 30 ♏, U.S.P.).

Spiritus Juniperi Compositus (U.S.P.).— A substitute for Holland Gin. A solution of oil of juniper, caraway, and fennel in 70% alcohol. *Dose:* to 15 c. c. (½ ounce) (8 c. c. = 2 ʒ, U.S.P.).

Buchu (U.S.P., B.P.).— The leaves of *Barosma betulina* and *B. crenulata.* Rutaceæ; Southern Africa. Contain a volatile oil, a glucosid, a bitter principle, etc.; 2 Gm. = 30 grs. Best given as infusion.

Fluidextractum Buchu (U.S.P.).— Three-fourths alcohol. *Dose:* 2 c. c. = 30 ♏.

Infusum Buchu (B.P.).— 5%. *Dose:* 30 to 65 c. c. (1 to 2 ounces).

Tinctura Buchu (B.P.).— 20%. Two-thirds alcohol. *Dose:* 2 to 4 c. c. (½ to 1 drachm).

Gnaphalium, Chamomile, and the *Aromatics* (see page 725) may also be used. These are given in the form of hot teas, and are also *Diaphoretic.*

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* Not official.
Study Materia Medica Lesson 10.
Study Materia Medica Lesson 11.

Volatile Oils Used Mainly in Diseases of the Respiratory Tract.

The volatile oils act as stimulants and antiseptics to the respiratory mucous membranes. They are applied to the nasal cavities by inhalation (eucalyptus), as sprays, or dissolved in oil, or as ointments (eucalyptus, thymol, menthol, camphor). They are used as expectorants in *chronic bronchitis.* They may be applied by inhalation (*e. g.*, turpentine, poured on boiling water, and inhaling the steam through a funnel). Others are taken internally, exerting their action in the course of their excretion through the lungs (Terebene, Terpin Hydrate, Pine Bark, Tolu, Grindelia).

They are also employed in *fibrinous pneumonia* and tuberculosis. Turpentine and its derivatives diminish excessive bronchial secretion in a rather specific manner, and are useful in certain cases of *cough and asthma.* It is claimed that they prevent experimental *tuberculosis* in dogs, but they have not been shown to be curative.

Ol. Terebinthinæ, especially by inhalation. *Pine Bark* is also used.

Terebenum (U.S.P., B.P.).— $C_{10}H_{16}$. A liquid, obtained by acting on Oil of Turpentine with concentrated H_2SO_4 and distilling. Only slightly soluble in water, but dissolved by three volumes of alcohol. *Dose:* 0.3 to 1.0 c. c. (5 to 15 minims) (0.5 c. c. = 8 ♏, U. S. P.); best given on sugar, or as inhalation.

Terpini Hydras (U.S.P.).— $C_{10}H_{18}(OH)_2 + H_2O$. Colorless crystals made by acting on oil of turpentine with alcohol and nitric acid. Soluble in 200 water, 10 alcohol. *Dose:* 0.1 to 1.0 Gm. (2 to 15 grains) (0.125 Gm. = 2 grs., U.S.P.). Also sometimes employed as urinary disinfectant.

Eucalyptus (U.S.P.).— The leaves of *Eucalyptus globulus,* Myrtaceæ. Australia; cultivated.

Contains a resin, volatile oil, etc.

Preparations:

Fluidextractum Eucalypti (U.S.P.).— Three-fourths alcohol. *Dose:* 2 c. c. = 30 ♏. Becomes turbid with water.

* *Elixir Eucalypti* (N.F.).— 1 : 8. *Dose:* 8 to 15 c. c. (2 to 4 drachms).

The above Eucalytus preparations are used mainly when the local (carminative) effect on the intestine is desired.

Oleum Eucalypti (U.S.P., B.P.).— The volatile oil. *Dose:* 0.3 to 2.0 c. c. (5 to 30 minims) (0.5 c. c. = 8 ♏, U.S.P.); or for inhalation.

Encalytol (U.S.P.) (Cineol, $C_{10}H_{18}O$).— Constitutes 50% of the oil. Colorless liquid. *Dose:* 0.3 c. c. = 5 ♏.

Eucalyptus oil is an active disinfectant, as well as a local irritant.

Oleum Cubebæ is commonly used; see above; so also is *Thymol,* see Index.

Balsamum Tolutanum (U.S.P., B.P.).— Its preparations are very popular as vehicles in cough mixtures, etc. It is a solid balsam, derived from *Toluifera Balsamum,* Leguminosæ; Venezuela. It is used as:

Syrupus Tolutanus (U.S.P., B.P.).— *Dose:* ad libitum (16 c.c. = 4 ℥, U. S. P.).

Tinctura Tolutana (U.S.P., B.P.).— 20%. *Dose:* 2 to 4 c. c. (½ to 1 drachm) (2 c.c. = 30 ♏, U.S.P.). With mucilage.

Grindelia (U.S.P.).— The leaves and flowering tops of *Grindelia robusta* and Gr. squariosa, Compositæ; western North America. Contains an amorphous resin (probably the active principle), sugars, proteids, tannin, and a very small quantity of volatile oil; no saponin or alkaloid (Power and Tutin, 1905).

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It is said to relax the muscular coats of the bronchi and diminish the excretion of mucus. It is therefore used in asthma. Its use in ivy-poisoning is mentioned on page 710.

Fluidextractum Grindeliæ (U.S.P.).— Three-fourths alcohol; precipitates with water. *Dose:* 2 c.c. = 30 ♏, U.S.P.

Eriodictyon (see Index) is also used in bronchitis.

Toxic and Ecbolic Volatile Oils.

All volatile oils are toxic in large doses. Direct systemic effects cannot be excluded altogether, but the phenomena are due almost exclusively to the local irritant action. The symptoms are mainly those of non-perforating *gastroentiritis* (see page 667). *Nephritis* is a common sequel. The extension of the gastroenteritis to the pelvic organs, with the consequent *ecbolic effects,* and its inherent dangers, were described on page 667. A mild degree of this action may be useful in delayed or painful menstruum, such as follows exposure to cold, etc. Large doses of the ecbolic oils, as also sassafras, rosemary, and thymol, cause fatty degeneration of organs (Heffter Lindemann).

Sabina (U.S.P.).— *Savin.*— The tops of *Juniperus Sabina,* Coniferæ. Temperate climates. The active ingredient is the volatile oil.

Fluidextractum Sabinæ (U.S.P.).— *Dose:* 0.3 c.c. = 5 ♏, U.S.P.

Oleum Sabinæ (U.S.P.).— The active volatile oil. *Dose:* 0.06 to 0.3 c.c. = 1 to 5 ♏. (0.05 c.c. = 1 m, U.S.P.).

Tanacetum.— *Tansy.*— The leaves and tops of *Tanacetum vulgare,* Compositæ; Europe and naturalized. *Dose:* 1 to 4 Gm. The active ingredient is the volatile oil.

* *Oleum Rutæ.*— *Oil of Rue.*— From *Ruta graveolens,* Rutaceæ; Europe and cultivated.

Hedeoma (U.S.P.).— The leaves and tops. 8 Gm. = 2ʒ (U.S.P.) Used as tea.

Oleum Hedeomæ (U.S.P.).— *Oil of Pennyroyal.* From *Hedeoma pulegiodes,* Labiatæ; North America. *Dose:* 0.06 to 0.3 c.c. = 1 to 5 ♏. (0.2 c.c. = 3 ♏, U.S.P.).

(It is the mildest of these agents, and is really more often used as a carminative.)

* *Apiol* is formed from oil of parsley by introducing some side-chains, amongst them allyl. It is very toxic, producing paralysis of the central nervous system and fatty degeneration of the liver and kidneys, besides its strongly irritant local actions. It was tried in amenorrhea, but has been discarded. *Dose:* 0.25 Gm. (4 grains), in capsules.

Volatile Oils Used in Dentistry.

A number of volatile oils (Cloves, Cinnamon, Sassafras, Gaultheria, Creosote, etc.) are used in dentistry to destroy the nerves of carious teeth and to disinfect cavities.

Insecticides.

Certain volatile oils, or drugs containing them, are used to kill or repel noxious insects, such as *Mosquitoes, Roaches, Flies,* etc. "Insect Powder" (the powdered flowers of Pyrethrum species — Persian Powder — and of Chrysanthemum cinerariæfolium — Dalmatian Powder); Eucalyptus, Menthol, Erigeron, Cedar, and Lavender may be cited. (Roach powders commonly contain borax; arsenic is efficient, but dangerous; White Hellebore is also poisonous.) Naphthalin and Camphor are used against *moths.*

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* Not official.

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Parasiticides Applicable to the Skin.— Allied to the cutaneous irritants are the drugs used to destroy parasites infesting the skin. Any antiseptic may be used for this purpose, provided it can be applied in oily solution. Against *bacterial and other vegetable organisms* (such as Trichophyton tonsurans) the most popular are the mercury preparations — Unguentum Hydrargyri Ammoniati, or Nitratis. Also sulphur, tar, and the various balsams. All these act, not only by killing the bacteria, but also by causing desquamation, removing the more superficial organisms mechanically, and exposing the deeper-lying parasites to the influence of the drugs.

Of *animal parasites* of the skin, Scabies, the "itch,"— Sarcoptis hominis,— is the most important. It is treated most efficiently with sulphur. Tar, Balsam of Peru, etc., are also used.

Against Pediculi, the best treatment — besides cleanliness — consists probably in Unguentum Hydrargyri. However, Insect Powders, Veratrin and the Sabadilla seeds containing it, Staphisagria, and Picrotoxinum are also used. The last are so poisonous, should they be absorbed, that they are not advisable.

MUSTARD OIL GROUP.

Mustard oil differs from the other volatile oils in that it produces a markedly greater irritation. The group also includes volatile oils derived from other cruciferous plants — horse-radish, onion, etc. The active principle of mustard is iso-sulpho-cyanid of allyl (CH_5CNS). This does not exist in the seed, but is formed from potassium myronate (sinigrin) in the presence of water under the influence of the ferment myrosin.

These oils are very diffusible, and, therefore, have a very deep action, without producing very profound destruction of the surface. Although they can produce very violent inflammation, the severe grades of action are so difficult to control that they are mainly useful when a mild but deep irritation is desired. The action must be watched very carefully. The oil is developed comparatively slowly, and one must not leave the mustard in contact with the skin until the desired grade of irritation is obtained, but remove it somewhat earlier.

MATERIA MEDICA.

Sinapis Alba (U. S. P., B. P.).— *White Mustard.*— The seed of Brassica alba, Cruciferæ; Europe and Asia. Cultivated.

Sinapis Nigra (U. S. P., B. P.).— *Black Mustard.*— The seed of Brassica nigra, Cruciferæ; Europe and Asia. Cultivated.

The emetic dose of mustard is 8 Gm. = 2 ʒ, in warm water.

The above contain 25% of bland fixed oil, gum, etc., the ferment Myrosin, and the white mustard *Sinalbin;* the black, *Sinigrin* (= Potassium Myronate). The latter yields, on the addition of water, the —

Oleum Sinapis Volatile (U. S. P., B. P.).— (Allyl sulpho-cyanid.) 8 mg. = 1/8 ♏, U. S. P. This is too irritant to be useful, but may be employed as —

Spiritus Sinapis (N. F.), 1 : 50; it also enters into the composition of *Linimentum Sinapis* (B. P.).

Mustard is, however, usually employed as the ground seed (mustard flour). The most convenient preparation is —

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Charta Sinapis (U. S. P., B. P.).—*Mustard Plaster.*—Made from black mustard previously exhausted of fixed oil by Benzin, made into a paste with a solution of india-rubber, and spread on paper. This is moistened with *luke-warm* water, and applied a quarter of an hour to one hour. A deeper action may be secured by the *Mustard poultice,* prepared by spreading a paste made with water and equal parts of mustard and flour on linen. Mustard is also used as an addition to hot foot-baths, being first made into a paste with warm water. Its use as emetic has been mentioned on page 314.

Other Cruciferæ contain similar oils, especially—

Armoraciæ Radix (B. P.)—The fresh root of *Cochlearia Armoracia, Horse-radish.*

The onion—*Allium Cepa;* and Garlic—*Allium sativum* (Liliaceæ), contain similar oils; the latter, Allyl sulphid.

Acrolein, the irritant vapors arising when fats are overheated, may also be counted in this group.

When mustard oil is heated with alcohol and ammonia, it loses its irritant odor and is converted into Allyl sulpho-carbamid, which, under the name of *Thiosinamin,* has been advanced as a cure for lupus. It is to be used by injecting 0.5 c. c. of a 10% solution in 20 parts of glycerin and 70 parts of water. The injection need not be made at the site of the lesion. It is also said to lead to the disappearance of cicatricial tissue. The clinical reports differ as to its value. It is a white, crystalline substance, soluble in 5 parts of alcohol, decomposed by water.

CANTHARIDIN GROUP.

A number of fixed organic drugs also act as local irritants. The most important of these is cantharidin. Capsicum, euphorbia, poison ivy, and croton oil, the "acrid principles" of certain fresh plants, especially of the family of Ranunculaceæ, etc., may be counted in this group. They owe their activity to neutral, resinous, or oily principles. Some benzol derivatives—chrysophanic acid, resorcin, pyrogallol, etc.—have a similar action, so also do some of the toxins.

Origin of Cantharidin.—Cantharidin is a crystalline principle, the anhydrid of cantharidic acid. It combines readily with alkalies, forming soluble salts. These produce the same local and systemic actions. Cantharidin is contained in a number of insects, especially beetles. A similar substance exists also in some caterpillars. It is present in varying amount, even in the same species. It was isolated by Robiquet in 1812 from the Spanish "Fly" (a beetle—Cantharis or Lytta vesicatoria). It is contained in the soft parts, particularly the blood. Cantharidin is not used as such, but as preparations made from the beetle.

Absorption and Excretion.—Cantharidin is readily absorbed from all surfaces. Even when applied to the skin, sufficient may be absorbed to irritate the kidneys, so that fly-blisters are contraindicated in nephritis. It is excreted mainly by the kidneys. It irritates the gastrointestinal tract even when injected hypodermically so that some must be excreted by this channel.

Local Actions of Cantharidin and Similar Drugs.—Vesication.—Cantharidin penetrates the epidermis quite readily, and produces violent but superficial irritation. This results in vesication. Very small quantities suffice for this purpose. $^1/_{10}$ mg. cantharidin or $^1/_{1000}$ mg. toxicodendrol will produce blisters on the human skin in the course of a few hours.

The weaker members of this group, or smaller amounts of the violent, will produce a superficial and very lasting irritant action. In this way they form useful complements to the volatile irritants, which latter produce a comparatively short action, and the two are very usefully combined. Tincture of capsicum is especially valuable for this purpose.

Gastroenteritis.— When taken by mouth, cantharides produce vesication of the lips, violent burning pain, vomiting, diarrhea, collapse, etc.

Cantharidin Nephritis.— The kidneys are extremely sensitive to cantharidin. Small doses act entirely on the glomeruli, which are enormously dilated; numerous leucocytes are found in Bowman's capsule. The urine becomes albuminous within half an hour after subcutaneous injection. The smallest doses increase its amount, while larger doses diminish it. The epithelium of the convoluted tubules is only affected by larger doses, and rather late in the course of the poisoning. The interstitial tissue escapes entirely in the acute intoxication, and is but slightly changed even in the subacute form (Mürset, 1886).

The bladder and urethra are also irritated and give rise reflex to *constant desire for micturation,* which is painful; *priapism,* etc.

The nephritis is the main cause of death in cantharides poisoning.

A very curious fact is the peculiar *immunity*[1] of the hedgehog, chicken, and duck to this nephritic action. This is not due to differences in the absorption, nor to destruction of the poison, for the cantharidin is found in the urine, just as it is in susceptible animals. Nor are these animals immune to other nephritic poisons. The immunity to cantharides is also only partial; even a single injection of a large dose causes chronic nephritis. But taking the fatal dose for man (30 mg. by stomach) as the unit, that for the same weight of hedgehog lies about 3,000. For the dog and cat it is about 2.5 (1 mg. per kilo); for the rabbit, about 45.

This immunity to the nephritic action does not confer immunity to the local action on the skin. In this respect, the hedgehog is even more susceptible than the rabbit, which latter animal is almost immune to the cutaneous action. The nephritic action is lessened by rendering the urine alkaline (Ellinger, 1905). In the rooster, cantharidin causes changes in the comb, analogous to those produced by ergot.

Central Actions.— When injected into the circulation, cantharidin affects the *central nervous system* in a manner similar to carbolic acid; *i. e.,* it produces short stimulation, excitement, and increased reflexes, followed by paralytic symptoms, coma, etc.

This central action is not often seen, being obscured by gastroenteritis or nephritis.

Therapeutic Uses.— Vesication.— Cantharis is the most useful of the vesicants.

The fresh Ranunculaceæ, mustard, or croton oil, are sometimes used by the laity, but their action is not so easily controlled as that of cantharis.

When the latter is contraindicated — *e. g.*, in cases of inflammation of the urinary passages,— it is usually replaced by ammonia water or chloroform, which also produce a vesicant action if their evaporation is prevented, as by covering the point of application by a thimble. These are rather more rapid in action, but much more painful than fly blister, and are, therefore, avoided, if possible.

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[1] Ellinger, 1900.

The vesicant action of cantharides develops rather slowly. It usually requires from five to ten hours. It can be somewhat hastened by removing the cantharides plaster after a few hours and applying a hot poultice.

Blisters in general are *contraindicated* in people of feeble condition, since they may then lead to ulceration. When they are employed for counterirritation, they should not be applied directly over the inflamed part, but at some distance from it. They might otherwise render the inflammation more violent.

Rubefaction.— Small quantities of cantharides, or the milder members of the group, form valuable additions to liniments, plasters, etc.

Cantharis is one of the most useful remedies in the treatment of **baldness.** It is used in the form of tincture, very greatly diluted with alcohol.

The best treatment for alopecia is prophylactic — frequent washing of the scalp with soap and hot water, followed by cold water. When the diseased condition has set in, there is fairly good prognosis if treated early; very poor, if treatment is begun late. If due to syphilis, the mercurials form the best treatment. Ordinary cases are treated by cutaneous irritants or astringents. Besides cantharides, the most useful are: Sulphur, resorcin, chrysarobin, salicylic acid, ammoniated mercury, calomel — all in 5% to 10% ointment or lotion — and alcohol. Pilocarpin is also supposed to stimulate the growth of hair by increasing the circulation of the scalp. If there is an active inflammatory condition, ichthyol or zinc oxid may prove useful.

Treatment of Impotence.— Very many drugs have been employed for this purpose, but our knowledge concerning them is still very meager. *Cantharis* is one of the most certain, acting through reflex irritation from the urethral mucous membrane. It is, however, quite dangerous, since effective doses are apt to set up considerable nephritis. Many *essential oils* act in the same manner, and are at once less dangerous and less active. Here belong, *e. g., damiana, ginseng, mint, garlic,* etc., and possibly *camphor.*

Strychnin is thought to be effective by raising the tone of the spinal centers.

Phosphorus and *arsenic* enjoy some reputation. If they are effective at all, it must be through improvement in the general condition of the patient.

Alcohol, morphin, cannabis, and other narcotics act as aphrodisiacs by stimulating the imagination. Yohimbin has a specific action.

The best treatment for impotence consists, of course, in the removal of the cause and improvement in the general health of the patient by appropriate hygiene.

MATERIA MEDICA OF CANTHARIDES GROUP.

Cantharis (U. S. P., B. P.).— *Cantharides.— Spanish Flies.*— The dried beetle, *Cantharis vesicatoria;* Insecta, Coleoptera; southern and central Europe.

The chief *constituents* are a volatile and fixed oil, extractives, and Cantharidin (0.4% to 1%); this is soluble in alcohol, ether, etc., and in oils.

The *dose of Cantharis* is 0.03 to 0.06 Gm. (½ to 1 grain).

Ceratum Cantharidis (U. S. P.) [*Emplastrum Cantharidis,* B. P.].—Contains 32%, with fats and turpentine. This, spread as a plaster, constitutes the Fly Plaster. It requires from six to ten hours to raise a blister, according to the thickness of the skin, its content in fat, and probably also individual susceptibility. Since cantharidin is insoluble in water, it is well that the skin be rather greasy, to facilitate its absorption. The plaster adheres very poorly, and must usually be fixed with adhesive plaster. When the blister has appeared, the plaster should be carefully removed without rupturing the vesicle. The latter is then pierced and dressed with an ointment. This prevents further pain, irritation, or infection. By a "flying blister" is meant a series of blisters raised along the course of a nerve by the application of successive plasters. The *Emplastrum Calefaciens* (B. P.) (Warming Plaster) is somewhat weaker.

Collodium Cantharidatum (U. S. P.) [*Collodium Vesicans,* B. P.].—*Cantharidal Collodion.*—60%. May be used instead of the plaster, being applied directly to the skin until it forms a rather thick pellicle.

Tinctura Cantharidis (U. S. P., 10%; B. P., 1¼%).—Alcohol. May be used as an addition to liniments (in any proportion) or internally, in *dose* 0.3 c.c. = 5 ♏ (U. S. P.).

Acetum Cantharidis (B. P.).—10% solution in 50% Acetic Acid.

Liquor Epispasticus (B. P.).—50% solution in Acetic Ether.

Unguentum Cantharidis (B. P.).—10% in Benzoinated Lard.

**Linimentum Cantharidis* (N. F.).—15% in Turpentine.

Other Drugs of the Cantharidin Series.—The actions and uses of these have been sufficiently discussed in the preceding section.

Capsicum (U. S. P.) [**Capsici Fructus,** B. P.].—(*Cayenne Pepper.*)—The fruit of *Capsicum fastigiatum* (U. S. P.) [*C. minimum,* B. P.]; Solanaceæ. Cultivated in tropical countries. The main constituents are: *Capsaicin* and volatile oils and resins, but imperfectly known.

Preparations:

Fluidextractum Capsici (U. S. P.).—Alcohol. *Dose:* 0.05 to 0.5 c.c. (1 to 8 drops) (0.05 c.c. = 1 ♏, U. S. P.).

Tinctura Capsici (U. S. P., B. P.).—10%. Alcohol. *Dose:* 0.3 to 4 c.c. (5 to 60 minims) (0.5 c.c. = 8 ♏, U. S. P.). In liniments, 1 : 15.

Oleoresina Capsici (U. S. P.).—Made with acetone (30 mg. = ½ gr.

Emplastrum (U. S. P.).

Unguentum Capsici (B. P.).

Mezereum (U. S. P., B. P.).—The bark of Daphne Mezereum (Thymelæaceæ, Europe and western Asia). The active constituent is the anhydrid of Mezerinic acid. There is also a glucosid, daphnin. 0.5 Gm. = 7½ grs.

Fluidextractum Mezerei (U. S. P.).—It is rarely used, as an addition to irritant liniments and plasters.

**Euphorbium.*—The dried juice of Euphorbia resinifera consists of a gum resin, the active constituent being the resinous euphorbon. The drug is rarely used (in liniments, 10%; plasters, 3%).

**Pulsatilla.*—The herb of Anemone Pulsatilla and A. pratensis; Ranunculaceæ, Europe. Should not be kept over one year. Active ingredient: Anemonin. The drug is very irritant, but it is used against asthma, hemicrania, etc., in *doses* of 0.1 to 0.4 Gm. It is almost obsolete.

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* Not official.

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Chrysarobinum (U. S. P., B. P.).— $C_{30}H_{26}O_7$; a compound of ***chrysophanic acid,*** obtained from *Araroba* (B. P.), Goa powder, found in cavities of the tree Andira Araroba, Leguminosæ. Powerfully irritant. Sol. in 4,812 water, 308 alcohol, 114 ether. A saturated ethereal solution of chrysarobin is used in the treatment of *warts.* It is painted on daily, the dead tissue being pared off. *Dose:* 30 mg. = ½ gr., U. S. P. (Goa powder contains 50 to 80% of chrysarobin. This can be converted into chrysophanic acid by oxidization.)

Unguentum Chrysarobini (U. S. P.).— 6%, in benz. lard; B. P., 4%.

Pyrogallol, resorcin, and salicylic acid are similar irritants. They are used in skin diseases and as parasiticides. (See Index.)

* ***Epicarin,*** a condensation product of cresotinic acid, is used as parasiticide, etc., like chrysarobin, in about double the strength.

POISON IVY.

A number of species of Rhus (Anacardiaceæ) produce violent dermatitis in sensitive individuals: Rhus vernix, synon. venenata (Poison Sumach, the most powerful); Rhus Toxicodendron (Poison Oak); Rhus diversiloba (Poison Ivy); Rhus pumila (a Southern species) — all common in North America; the Japanese lacquer tree (Rhus vernicifera). The common sumach, Rhus glabra, does not have this action. A number of tropical trees belonging to the same family also cause dermatitis — Lithrea caustica; Anacardium (active principle, cardol, an oily substance); Semecarpus. Primula, chrysanthemum, arbor vitæ, and many other plants affect sensitive persons in the same manner.

Accidental Ivy-poisoning is quite common, since these plants are of frequent occurrence along the roadside, on fences, in swamps, etc.

Only certain individuals seem to be susceptible to the poisoning, while others may handle or masticate all portions of the plant with absolute impunity. The reason for this difference is very obscure, but it may be remembered that certain animals are immune to cantharidis. The tolerance may be merely relative. In susceptible individuals an extremely small amount of the poisonous principle (1/1000 mg.) is sufficient to cause a violent dermatitis. In this way the poisoning may be spread by *contagion; i. e.,* sufficient may be passed from the clothing or hands of one person to another to cause poisoning. This is, perhaps, the only instance of contagion by a chemic poison.

The toxic principle was long believed to be a volatile acid, but later investigations have shown that it is neither an acid nor volatile, but a fixed oil (*toxicodendrol*) (Pfaff).

The authenticated cases of poisoning at a distance, which would seem to speak for its volatility, can probably be explained by the oil being carried by dust, pollen, etc. The toxicodendrol occurs in the lacteal vessels, which terminate in fine hairs (Schwalbe, 1902).

The active principle is the same for all the species. It has a considerable latent period, from one to nine days, usually four to five days. This does not seem to be influenced by the dose. The action consists in a typical dermatitis, passing through all the successive stages, from hyperemia with itching, to vesication and pustulation.

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* Not official.

Taken internally, it is an active irritant, exerting its strongest action upon the kidneys.

The toxic principle is destroyed by alkalies. It forms comparatively insoluble compounds with lead. The methods of *treatment,* therefore, consist either in applying to the skin a paste made with an alkali, preferably castile soap, or else a solution of lead acetate, preferably in alcohol, to loosen the oil. Fluid extract of *Grindelia robusta,* diluted with 4 to 8 volumes of water and used as a wash, is frequently useful.

The expressed juice of Impatiens fulva is also said to be curative when applied to the skin. Copper and iron salts are also useful.

The very worst treatment which can be imagined is the application of vaselin or other ointments, since they dissolve out the toxicodendrol and tend to spread it over a larger surface.

OTHER FORMS OF COUNTERIRRITATION (MAINLY PHYSICAL.

Any agent capable of producing inflammatory reaction may be employed for counterirritation. These remaining forms of irritation are mainly as follows:

1. Bacterial.
2. Friction (Exercise, Massage), Acupuncture, Scarification.
3. Temperature.
4. Electricity.
5. Venesection.

1. Bacterial Counterirritation.— This method is at present practically obsolete. It was formerly accomplished with setons — a string of some fibrous material was carried through a fold of skin and left there to suppurate. More recently, bacterial counterirritation has been employed in the form of artificial streptococcus infection against various tumors.

2. Friction.— This acts partly by producing hyperemia, partly by massage. The benefit derived from liniments is partly due to the friction used in their application.

Exercise and Massage.— Although counterirritation or other reflex stimulation is only in small part responsible for the effects of exercise and massage, those effects bear in some particulars a sufficiently close resemblance to those of counterirritation to excuse their discussion in this place.

The stimulating effect of **exercise** ***in health,*** and its use for the preservation of this, and for the development of the body, etc., must be left for text-books of physiology and hygiene.

It is applied to diseases mainly in the form of *Swedish movement and massage.*

The **Swedish movement** consists in contracting the muscles against resistance furnished by the operator.

Its advantage over ordinary exercise lies in the exactness with which the effort may be regulated and in the possibility of confining the work to particular muscles.

In **massage** the patient is entirely passive, the muscles being treated by the masseur (or masseuse).

The muscles are put into a state of semiflexion and subjected to a manipulation, generally in centripetal direction. The various movements consist in stroking, kneading, friction, percussion, and their modifications, according to the effect which it is intended to produce.

The results depend upon counterirritation, local changes in the circulation and metabolism, reflex effects upon the central nervous system, and the results of exercise in improving the general nutrition.

To produce the reflex results, light stroking or percussion is employed.

Kneading is more efficient to relieve local swellings or edemas. It is easy to convince one's self of the importance of this when one remembers the rapidity with which the swelling from a hypodermic injection may be made to disappear under manipulation. The venous circulation, and especially the lymphatic circulation in muscles, are influenced very largely by the muscular movements, and are in this way greatly increased by exercise, and still more by massage.

A combination of all the movements is used when it is desired to influence the general nutrition of the patient, to supply general exercise, or to prevent atrophy of the muscles in paralysis, or to break up adhesions, etc.

Acupuncture is the process of pushing needles through the skin into the underlying organs. It sets up a certain amount of inflammatory reaction. This method of treatment is much in favor among the Chinese. It is practically obsolete among other civilized peoples.

Scarification is the process of making small incisions with a knife or needles. Irritants, as croton oil, may be rubbed into the resulting wounds, and the action of the drugs will so be considerably increased.

3. Temperature — Hydrotherapy.—

The effects of baths are so largely due to the heat or cold that these may be included under the general heading of Hydrotherapy. The treatment of disease by these means is really a very ancient practice, alternately popular and neglected, and which has undergone a considerable revival in the nineteenth century. It has been developed so extensively as to constitute a special branch of Therapeutics, and its treatise in detail must be left to larger works.

The effects of heat and cold present a certain amount of similarity, both being irritants. They lead to dermatitis of all degrees, from simple temporary hyperemia to corrosion. The results of this counterirritation are mainly nervous, at once sedative and invigorating. They seem to favor digestion, oxidation, and sleep. They increase the excretion of nitrogen (except Russian steam-baths, and, in exceptional cases, tepid salt water baths).

The application of heat acts, of course, as a diaphoretic.

(A) General Effects of Cold Baths; *i. e., those having a temperature near or below 70° F.* (21° C.).

These produce at first a contraction of the cutaneous vessels and, in consequence, a sensation of *chilliness.* The *respiration* is reflexly increased and becomes gasping. If the patient is kept in the water, the body-temperature may be somewhat reduced, especially when it is abnormally high. In this case the fall will continue for a little time after the patient has left the bath. As soon as the cold is removed the cutaneous vessels will often dilate very rapidly, bringing an abnormally large amount of blood to the surface. This is usually the case when the skin is vigorously rubbed. The former, the reduction of temperature, determines the usefulness of cold baths in *fever*. The latter, the effect on the cutaneous vessels, acts as a *tonic*. The exercise which this affords to these vessels also serves to harden the body against *exposure*.

When used on persons with feeble circulation, cold baths are apt to do harm rather than good.

Where cold baths are not practicable, they may be replaced by *cold affusions, cold sponging,* or by the *cold pack*. In the latter the patient is wrapped in a wet sheet wrung out of cold water, and is then packed in several blankets.

Cold has the same effects when it is restricted to **limited areas.** This may be done either in the form of *compresses* wrung out of cold water or by means of the *ice-bag*. These not only seem to be useful counterirritants, but also appear to *lessen inflammation directly* by producing constriction of the vessels. *Cold foot-baths* are very efficient in checking the menstrual flow. *Cracked ice* taken by the mouth is one of the most efficient means of relieving vomiting. A more intense cold and artificial freezing of the tissues are employed as *local anesthetics.*

(B) Heat may be applied either dry or moist.

1. **Sun Bath.**—The direct rays of the sun produce an active hyperemia of the cutaneous vessels and may lead to dermatitis. Similarly the X-rays, which have found therapeutic application for this purpose.

They produce all grades of dermatitis according to the time during which they are applied and to the susceptibility of the individual.

Sunlight exerts a very conspicuous *tonic effect*. This is indeed in great part psychic; but the oxidizing power is greater in sunlight than in the dark, even in the case of excised tissues.

2. When it is desired to have the action of heat confined to limited areas, this is usually accomplished by *hot-water bags* or **poultices.**

The peculiar advantage of the poultice lies in its applying heat without changing the natural moisture of the skin. The oily basis of the poultice will neither macerate the epidermis nor allow it to lose water. The oil also aids in retaining the heat of the poultice, so that its action extends more deeply than by any other method and with less injury to the superficial layers. A poultice, to be useful, must be very hot, so hot that it needs to be separated from the skin by a few layers of flannel. (For methods of preparing poultices see p. 71.)

3. A somewhat similar result can be attained by wet **compresses** covered by india-rubber or gutta-percha, to prevent evaporation. In this way the body is made to furnish the heat.

4. When the application of dry heat is intended to be more general, it may be used in the form of the **hot-air bath.**

This is one of the most efficient diaphoretic measures. The simplest form of application is to cover the patient with an abundant supply of blankets in a hot room. Other forms are the *Turkish bath*, or the patient may be seated on a chair, enveloped in a blanket, and an alcoholic lamp placed under the seat of the chair.

The application of *very hot dry air* to joints has been found very useful in chronic rheumatism. It requires special apparatus and experience.

5. The application of intense heat leads to **cautery.** According to the apparatus used, this is spoken of as *thermocautery* or *galvanocautery*.

A somewhat ancient form of producing a deep but very powerful and painful counterirritation is by placing an ignited *moxa,* a small cone of inflammable material, on the skin.

Moist Heat.—General Warm Baths.

The results of baths will vary with their temperature. *Warm baths* are those with temperatures ranging from 36° to 29° C. (97° to 85° F.). *Hot baths* are above this temperature.

The *warm baths* are used mainly to lessen internal congestion. By dilating the cutaneous vessels they bring more blood to the surface, and so may even reduce the temperature, and may be employed in fevers. By drawing blood from the brain they are useful in insomnia, etc. *Hot baths* may lead to an actual rise in the temperature of the body if they are sufficiently prolonged. They are only used to produce diaphoresis.

Baths may be rendered more specific in their action on the skin by the addition of various medicinal agents, forming **Medicated Baths.** *Salt,* especially sea salt, in the proportion of 2% to 4%, increases the counterirritation. *Acid* baths are used when a more intense action is desired, with the minimum effect on the epithelium. *Alkaline* and *sulphur* baths are useful in certain skin diseases in which the epithelium is thickened. They are also employed in rheumatism, where their effect must be reflex. General *mustard* baths were formerly used to quicken the appearance of the eruption in exanthemata. They are at present very little employed. They were prepared by adding mustard to water in the proportion of about ½ to 1 teaspoonful to a gallon. The patient is left in this bath only until he feels the first burning in the skin.

Local baths are sometimes employed for the relief of pain or to change the blood supply of a part. This may generally be accomplished more effectually by poultices or hot-water bags. An exception are hot *foot-baths.* These cause a vasomotor dilatation not only in the feet, but also in the whole splanchnic area. They are therefore useful to restore the menstrual flow. They also lessen congestion in the lungs.

The effects of *Russian or steam-baths* are very similar to hot-water baths.

The *Kneip curc,* consisting in walking through wet grass with bare feet, is essentially a cold foot-bath.

4. Electricity.—

The use of electricity in the diagnosis and therapeutics of diseases of the *peripheral nerves* has become so complicated as to be beyond the limits of this treatise. Briefly, the *indications* for its use are to produce irritation or counterirritation, or to prevent atrophy of muscles. The counterirritation is especially valuable in chronic rheumatism. It is employed here in the form of the faradic current. It is also said to be a useful irritant in alopecia, when it is applied in the form of brush electrodes.

5. Venesection, Cupping, and Leeches.[1]—

The effects of these also consist in the change in the distribution of the blood. They are therefore analogous to counterirritation.

---

[1] *Leeches* (Hirudo) are applied by holding them to the skin, which has been moistened with milk. They fix themselves, make a peculiar triradiate cut with

It has already been pointed out that the effect of subcutaneous and intravenous *injection of normal salt solutions* is somewhat in the nature of a counterirritation, by chemic stimulation of the vascular endothelium.

6. Cathode Rays and Radioactive Metals.—

(Radium, uranium, barium, thorium, bismuth, etc.).

The rays emitted from these metals, and the cathode rays, appear to act in an identical manner. They are destructively irritant. They lead to pronounced degenerative lesions of the skin — dermatitis, deep and slowly healing ulcers — and in superficially seated pathologic tissues (epithelionia, lupus, etc.).

The *skin lesions* are produced by active preparations after an exposure of 5 to 20 minutes, but a latent period of some days or weeks elapses before the changes become noticeable. Similar, but much milder, changes are produced in exposed *mucous membranes* (Rehus, 1904). The effects on other exposed *tissues* are also similar, but milder (Schwarz, 1903). They are always preceded by a latent period. Bouchard (1904) saw marked *pulmonary congestion* following the inhalation. *Small animals* die with convulsions and coma when exposed (*e. g.*, Bogrow, 1903). Most *invertebrate animals* are rapidly killed (Willcock, 1904); *bacteria* are scarcely affected (Beurren and Zinser, 1903; Prescott, 1904).

The effect on *embryos* is more powerful; it arrests development or causes deformities of the larvæ of ascaris, sea urchins, frogs, toads, etc. (Bohn, Bogrow, 1903; Perthes, 1904). It also causes atrophy of the *ovary of mammals* (Rabbit; Halberstaedter, 1905), and seems to produce *sterility,* at least temporarily, in males.

The effect on *ova* has been studied by G. Schwarz (1903) on the chicken egg. The principle effect is on the yolk, which becomes discolored, and acquires the taste and odor of decomposing lecithin. He shows that the changes are not due to heat; and is inclined to attribute the physiologic effects of radium to changes in the tissue lecithin. As an extension of this theory, Werner (1905) claims to produce the typical radium skin-changes by the subcutaneous injection of lecithin which has been previously decomposed by exposure to radium or Roentgen rays. This statement needs further confirmation. Radium is capable of inducing powerful chemic changes, which might explain its actions. Henri and Mayer (1904) have also shown that it precipitates positively charged colloids, so that we may be dealing with an electron effect.

Radiotherapy is still experimental. It is being tried for the cauterization of lupus and other superficial malignant tumors, and in milder grades for counterirritation in neuralgia, etc. The action is confined to the surface.

The *intravenous injection* of radium salts causes circulatory changes, closely resembling those of barium, and perhaps due to this contamination (Burton-Opitz and Meyer). The metabolism is scarcely altered (Berg and Welker). All organs show radioactivity, especially the blood (Meyer).

Fluorescent Substances.— V. Tappeiner and Raab (1903) have found the fluorescent substances are very destructive to all forms of life, and also to ferments and toxins; but that the effects appear only in the presence of the specific light rays which induce the fluorescence.

their mouth, and draw about 5 to 7 c. c. of blood. This quantity may be somewhat increased by applying hot fomentations after removing the animal. Their purpose can usually be better served by cupping.

RESUME OF THERAPEUTICS OF SKIN IRRITANTS.

I. Therapeutic Classification.— These irritants may be divided, according to the extent and manner of their action, into the following classes:

1. Extensive and superficial, without injury to the epidermis: baths, especially salt-water baths.

2. Extensive and superficial, with softening of the epidermis: sulphur and alkali baths.

3. Local, deep, nutritive: iodin, etc.

4. Local, superficial, nutritive: metallic salts, etc.

5. Local, superficial, sensory, brief: volatile oils, turpentine, chloroform, aconite, etc.

6. Local, deep, sensory, lasting: capsicum, caustics (used only in veterinary practice); vesicants: cantharides, ammonia, chloroform.

II. The **indications** for skin irritants may be summarized as follows:

1. In skin diseases.
2. To produce diaphoresis.
3. To reflexly affect the central nervous system, especially the medulla. The volatile irritants are here the most useful.
4. As counterirritants:

(*a*) To change the distribution of the blood and thereby diminish deep chronic inflammation.

(*b*) In a similar manner to remove inflammatory exsudates from the connective tissue.

(*c*) To diminish pain.

(*d*) As a tonic to the whole body.

III. Explanatory.— **1.** For their use in *skin diseases,* see Chapter XXXI, B.

2. For use as *diaphoretics,* see page 282.

3. As reflex irritants of the central nervous system:

To make this subject clear it will suffice to recall the effects of stimulation of the central end of the *sciatic nerve.* A moderate stimulation of this kind produces, reflexly, a slowing of the heart through stimulation of the vagus center; a rise of blood pressure through vasomotor stimulation; and increased respiration through stimulation of the respiratory center. A much stronger stimulation may have precisely the opposite effect; *i. e.,* depress these centers.

Counterirritants produce analogous phenomena:

Milder degrees of this action are useful in resuscitating patients from *syncope* or from *profound anesthesia.* The quickest effect may be obtained either by giving the irritant hypodermically, or by inhaling a volatile irritant, in which case it acts through the trigeminal. One may also employ electricity, or heat or cold applied to the skin.

4. (a) and **(b) To affect the distribution of blood:** Local changes in the circulation at points remote from the seat of application of the irritant, arise either directly through continuity with the seat of irritation, or through reflexes. By continuity, an increased vascularity of the skin may influence the circulation in neighboring organs in two opposite ways: It either causes hyperemia of the organs simultaneously with its own hyperemia, or it may draw blood from these organs and thus cause them to become anemic.

We see a hyperemia of this kind in the case of the pelvic organs when the intestinal canal is irritated, whereas this same irritation causes an anemia of the cerebral organs.

Reflexly, changes in the caliber of vessels of cutaneous areas may affect the vascularity of organs at a distance, through the vasomotor centers; *e. g.*, hot and cold foot-baths will react upon the circulation within the pelvic organs.

To affect the vascularity of the skin, deeply acting and lasting stimulation will be required, as also for the removal of inflammatory products.

4 (c). **To diminish pain:** It has long been known that the application of heat or counterirritants in certain limited superficial situations modifies painful impressions and inflammatory processes in internal organs.

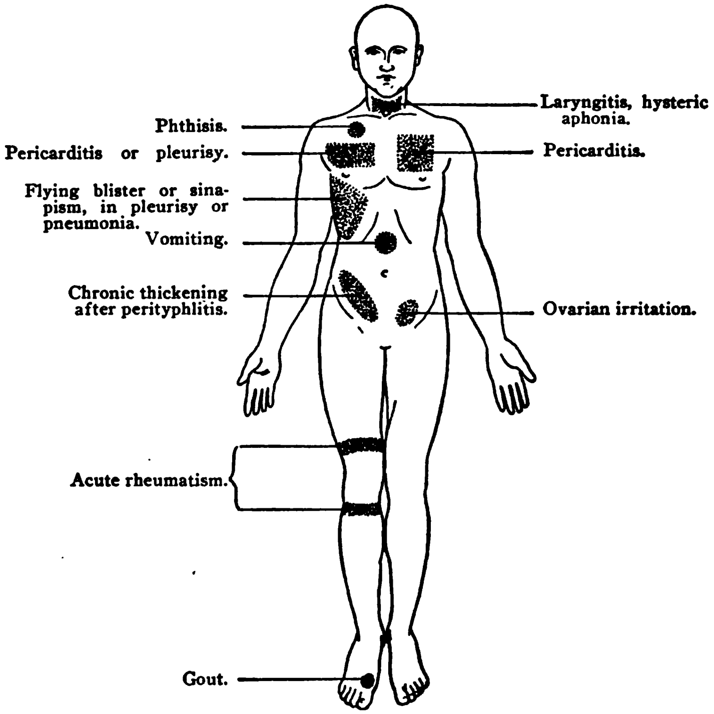
Laryngitis, hysteric aphonia.
Phthisis.
Pericarditis or pleurisy.
Pericarditis.
Flying blister or sinapism, in pleurisy or pneumonia.
Vomiting.
Chronic thickening after perityphlitis.
Ovarian irritation.
Acute rheumatism.
Gout.

Fig. 93.— Diagram of the body showing some of the points where blisters or sinapisms are usually applied. Front view.—(*Brunton.*)

These observations were entirely empirical, but some light has recently been thrown on this subject by the results of Head on the innervation of viscera.

Head comes to the conclusion that the internal organs and definite portions of the surface of the body receive their nerve supply from the same spinal segments, and that irritation of the one will react upon the other. It is remarkable how closely the areas which he mapped out experimentally as corresponding to the internal organs correspond to those positions on which the application of counterirritation has been found empirically most useful (Figs. 93 and 94).

Counterirritation is, as a rule, useful only in chronic inflammation. In acute inflammation there is always a danger of increasing the process or of causing it to extend to neighboring organs.

Liniments: Cutaneous counterirritants are usually employed in the form of liniments; *i. e.,* in solution or suspension in oil or alcohol. The proportions in which they are used are the following:

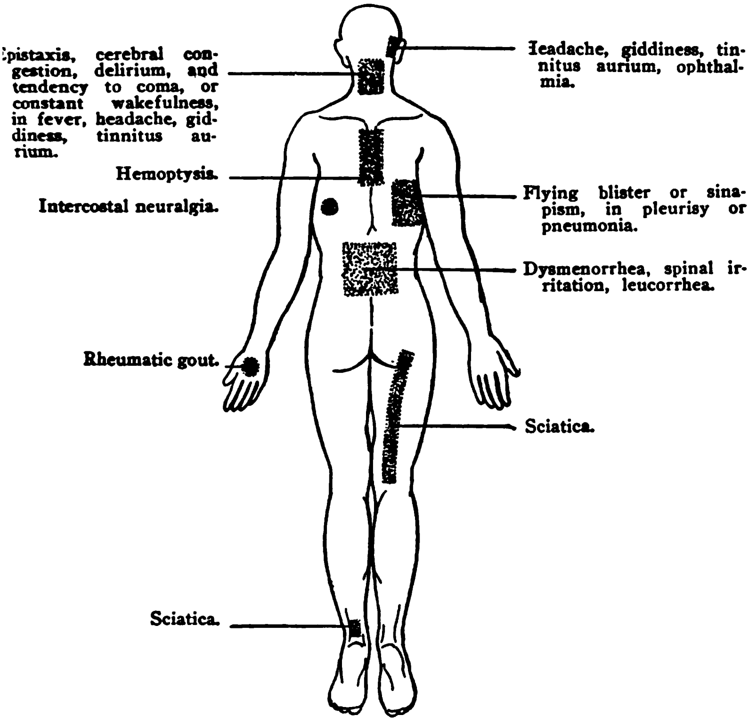
Epistaxis, cerebral congestion, delirium, and tendency to coma, or constant wakefulness, in fever, headache, giddiness, tinnitus aurium.
Hemoptysis.
Intercostal neuralgia.
Rheumatic gout.
Sciatica.
Headache, giddiness, tinnitus aurium, ophthalmia.
Flying blister or sinapism, in pleurisy or pneumonia.
Dysmenorrhea, spinal irritation, leucorrhea.
Sciatica.

Fig. 94.—Diagram of the body showing some of the points where blisters or sinapisms are usually applied. Back view.—(*Brunton.*)

Ammonia Water	1 : 5.
Tr. Belladonna or Opium, etc.	
Spirits Chloroform	
Spirits Ether	
Spirits Camphor	
Tr. Iodin	
Tr. Aconite	
Tr. Capsicum	1 : 10.
Tr. Cantharides	
Turpentine	
Sp. Sinapis	
Essential Oils	
Croton Oil	1 : 50.
Creosote	

TABLE XV.—LINIMENTS.

The Official Liniments are very good representatives of this class of preparations. The composition of the principal ones is as follows:

	U. S. P.	B. P.
Linimentum Ammoniæ:	Ammonia Water. 35 Alcohol .... 5 Cotton-seed Oil. 57 Oleic Acid 3	Ammonia Water. 25 Olive Oil ...... 50 Almond Oil 25
Lin. Belladonnæ:	Camphor .... 5 Fldext. Belladonna Root, to 100	F. E. Belladonna .... 50 Camphor .... 5 Alcohol 50
Lin. Calcis: (Carron Oil)	Lime-water, Linseed Oil, } equal parts.	Lime-water, Olive Oil, } equal parts.
Lin. Camphoræ: (Camphorated Oil)	Camphor ...... 20 Cotton-seed Oil. 80	Camphor .... 25 Cotton-seed Oil. 75
Lin. Chloroformi:	Chloroform .... 30 Soap Liniment . 70	Chloroform .... 50 Camphor Liniment 50
Lin. Saponis: (Soap Liniment)	Soap .... 60 Camphor .... 45 Oil Rosemary .. 10 Alcohol ....725 Water .....to 1000	Soap ....100 Camphor .... 50 Oil Rosemary... 20 Alcohol ....850 Water .....to 1000

This is practically identical with "Opodeldoc."

	U. S. P.	B. P.
Lin. Saponis Mollis: (Tinctura Saponis Viridis)	Soft Soap...... 65 Oil Lavender ... 2 Alcohol .... 30 Water ......to 100	
Lin. Terebinthinæ:	Resin Cerate ... 65 Oil Turpentine.. 35	Camphor .... 5 Soft Soap....... 75 Water .... 25 Oil Turpentine . 65

To these may be added the following National Formulary Preparations:

Lin. Aconiti et Chloroformi:	Tr. Aconite .... 1 Chloroform .... 1 Soap Liniment 6
Lin. Cantharidis:	A 15% solution in oil of turpentine.
Lin. Iodi:	Iodin ....12.5 KI .... 5.0 Glycerin .... 3.5 Water .... 6.5 Alcohol ....to 100.0

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Lin. Sinapis Compositum:

Mustard Oil	3
Fldext. Mezereum	20
Camphor	6
Castor Oil	15
Alcohol	to 100

Also the B.P. Preparations:

Linimentum Camphoræ Ammoniatum:

Stronger Ammonia	10
Camphor	5
Lavender Oil	¼
Alcohol	to 40

Linimentum Crotonis:

Croton Oil	1.0
Cajeput Oil	3.5
Castor Oil	3.5

Linimentum Aconiti:

Aconite	60
Alcohol	to 100
Camphor	5

Linimentum Sinapis:

Vol. Oil Mustard	2
Camphor	3
Castor Oil	7
Alcohol	43

Linimentum Terebinthinæ Aceticum:

Turpentine	4
Glacial Acetic Acid	1
Camphor Liniment	4

The plasters are also irritant. They are discussed in Chapter XXXI.

CHAPTER XXX.

SPECIFIC IRRITANTS OF THE ALIMENTARY CANAL.

(INCLUDING ANTHELMINICS).

It has already been pointed out that certain irritant substances confine their action mainly to the alimentary canal. These are the *Stomachics, Carminatives, and Vegetable Cathartics.*

(A) STOMACHICS.

These may be *defined* as drugs which favorably modify the digestive process in various functional disorders, and whose action rests neither on a chemic nor on a physical basis.[1]

These substances are characterized by a marked and sharp taste, either *bitter* or "*aromatic.*"

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[1] The last portion of the definition excludes ferments, acids and alkalies, and salts.

A mixture of the two gives the "*aromatic bitters.*" If the bitters also contain tannin, they are called "*astringent bitters.*"

Manner of Action: It has been found, in animal experiments, that stomachics *increase absorption* (of sugar or peptone) from the stomach and intestines; Brandl, 1893. The *secretion* of the gastric and pancreatic juice is also increased. The gastric fluid contains more acid, ferment, and chlorids. These results *follow in half an hour* after the drugs are given, their immediate action being almost nothing, or slightly in the opposite direction. The mechanism by which these results are secured is not perfectly understood. However, there is no doubt that the effects *depend mainly on a mild and peculiar irritation*, producing a reflex flow of all digestive fluids (and probably also an increased production of secretin); a beneficial hypermia of the mucous membranes; and a stimulation of the motor-functions of the alimentary canal. The *increased appetite* which is noticed may be accounted for by a stimulation of the nerve endings concerned in the sensation of hunger.

Experiments with dogs provided with esophageal, gastric and Pawlow fistulas have given the following results:

The administration of bitters alone has no effect; but when this is followed by a meal within twenty minutes (*i. e.*, whilst the bitter taste is still present), the flow of gastric juice is increased by 15 to 40%. This has the normal composition. The same results are obtained if the bitter and food are prevented from reaching the stomach by an esophageal fistula (Borisoff, 1904). This shows that the effects are produced mainly from the mouth; the most plausible explanation being, that the bitter taste puts the taste-organs into a condition in which they appreciate the taste of food more highly, thereby favoring the reflex secretion of gastric juice.

If the feeding is delayed for longer than half an hour, the bitters are quite ineffective. Somewhat larger doses are also without action; whilst still larger doses actually diminish the secretion, this effect lasting for several days. (Strashesko, 1905).

Hoppe (1905) adduces some evidence that the presence of the bitter substance in the stomach also sets up a reflex, increasing the flow, and generally the acidity. With condurango, the increased flow is especially marked, but the acidity is not raised. Orexin was effective in chronic gastritis with hyperacidity, but had no action on the normal stomach.

Bitters and aromatics are also markedly antiseptic, and may therefore influence digestion favorably by limiting putrefaction and abnormal fermentation.

A further action of stomachics (both bitters and aromatics) which may be concerned in their therapeutic action, is that they *increase the leucocytes* of the blood. (Hirt, Binz, Pohl). The theory has been advanced that these leucocytes play a rôle in intestinal absorption. (Hofmeister, 1887).

Very similar results are obtained by alcohol and by the various condiments — salt; acid, as in vinegar; sharp, as in mustard, etc.

The use of these substances dates from the most ancient times, and the "spices of the orient" have played a considerable rôle in the commercial history of the globe. The bitter substances have held, and still hold, a very prominent place in popular medicine.[1]

Their **uses** may be summarized as follows:

1. To modify or improve the taste of food or medicines; also to obscure a "bad taste in the mouth."
2. To increase digestion in cases of overeating, either by overindulgence in the pleasures of the table, or when it is desired to subject a patient to "forced feeding." In the latter case they act as *tonics*.
3. To increase appetite, from whatever cause this be deficient.
4. To improve digestion in all kinds of "atonic" dyspepsias.
5. As antemetics.

Stomachics are always administered half an hour or an hour before meals. If there is a catarrhal condition,— *i. e.*, a subacute or chronic inflammation,— the *tannin* of the astringent bitters is apt to be very useful. Ordinarily it is not so. It must be especially avoided when the bitter is to be prescribed with iron, since this makes an unsightly mixture. Tannin-free are the simple bitters and the majority of the aromatic bitters. Pharmacists have attempted to prepare "detannated tinctures," by precipitating the tannin with iron, gelatin, hide, etc. But so far these are not very successful.

What, if any, differences exist between bitters and aromatics is not known. It has been found, however, that their action and taste can be greatly improved by judicious blending, as in the compound bitters.

In this class of stomachics comes properly a new synthetic compound, **Orexin.** Its tannate is practically tasteless and insoluble, and yet it is said to exert a very pronounced action in increasing appetite and digestion, somewhat like the group just discussed. It also prevents the distress which follows the eating of certain substances — such as radishes, etc.— in individuals who have an idiosyncrasy against them. *Dose:* 0.1 to 0.4 Gm. (2 to 6 grains) in powders, before meals. It is contraindicated in hyperacidity and in gastritis. The clinical results are not very favorable.

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[1] About a tenth of the medicines mentioned by Hippocrates belong to the class of bitters.

(B) CARMINATIVES.

This class comprises certain aromatic oils exerting an irritant action upon the stomach intestine, being somewhat specific in causing the expulsion of gas rather than of fluid or solid contents. Since they are also antiseptic, they are especially useful in abnormal fermentation, removing at once the discomfort caused by the gas, and checking the growth of the bacteria which give rise to it. They also form useful addition to laxative mixtures, since they diminish the "griping."

MATERIA MEDICA OF STOMACHICS AND CARMINATIVES.

The number of bitter substances and carminatives is so excessively large that space will permit of the enumeration of only the most important. They will be subdivided as in the text.

I. Simple Bitters.

(*i. e.*, practically free from aromatic oils or tannin). Can be mixed with water.

The tinctures have for the most part a strength of 20%. The *doses* are those of the U. S. P. (Tinctures, 4 c. c. = 1 ʒ; fldexts., 1 c. c. = 15 ♏.)

The *pure alkaloids*, especially

Quinin Sulphate, 0.05 Gm. (1 grain); *Strychnin Sulphate*, 0.001 Gm. ($^1/_{60}$ grain); *Berberin sulphate*, 0.1 to 0.3 Gm. (2 to 5 grains).

Calumba (U. S. P., B. P.).—*Colombo.*—The root of *Jateorrhiza palmata*, Menispermaceæ. Eastern Africa; cultivated in East India islands.

Preparations:

Fluidextractum Calumbæ (U. S. P.).—*Dose:* 2 c. c. = 30 ♏.

Tinctura Calumbæ (U. S. P., B. P.).—20%. *Dose:* 4 c. c. = 1 ʒ.

Infusum Calumbæ (B. P.).—*Dose:* 15 to 30 c. c. (½ to 1 oz.).

Gentiana[1] (U. S. P.).—*Gentian.*—The root of *Gentiana lutea*, Gentianeæ. Switzerland. Gentiopicrin, $C_{16}H_{20}O_9$; Gentiin, $C_{25}H_{28}O_{14}$.

Preparations:

Extractum Gentianæ (U. S. P., B. P.).—Pilular. Used as pill excipient. 0.25 Gm. = 4 grs.

Fluidextractum Gentianæ (U. S. P.).—*Dose:* 1 c. c. = 15 ♏.

Tinctura Gentianæ Composita (U. S. P., B. P.).—10%; with Bitter Orange Peel and Cardamon. Dose: 4 c. c. = 1 ʒ.

Elixir Gentianæ (N. F.).—3.5%; detannated by iron. *Dose:* 8 to 30 c. c. (2 to 8 drachms).

Infusum Gentianæ Compositum (B. P.).—Contains Bitter Orange Peel and Lemon Peel. *Dose:* 15 to 30 c. c. (½ to 1 oz.).

Quassia (U. S. P., B. P.).—The wood of *Picræna excelsa*, Simarubeæ. Jamaica.

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[1] Gentian contains a small amount of Tannin; not enough to make it astringent, but sufficient to cause a discoloration with iron.

Preparations:

Extractum Quassiæ (U. S. P.).— Powdered. *Dose:* 0.065 Gm. = 1 gr.

Fluidextractum Quassiæ (U. S. P.).— *Dose:* 0.5 c. c. = 8 ♏.

Tinctura Quassiæ (U. S. P., B. P.).— 20%. *Dose:* 2 c. c. = 30 ♏.

Infusum Quassiæ (B. P.).— 1% in *cold* water. *Dose:* 15 to 30 c. c. (½ to 1 oz.).

Liquor Quassiæ Concentratus (B. P.).— 10%. *Dose:* 2 to 4 c. c. (½ to 1 drachm).

Chirata (U. S. P., B. P.).— The entire plant of *Swertia Chirata,* Gentianeæ. Northern India.

Preparations:

Fluidextractum Chiratæ (U. S. P.).— *Dose:* 1 c. c. = 15 ♏.

Tinctura Chiratæ (B. P.).— 10%. *Dose:* 2.0 to 8.0 c. c. (½ to 2 drachms).

Liquor Chiratæ Concentratus (B. P.).— 50%. *Dose:* 2 to 4 c. c. (½ to 1 drachm).

Infusum Chiratæ (B. P.).— 5%. *Dose:* 15 to 30 c. c. (½ to 1 oz.).

Taraxacum (U. S. P., B. P.).— *Dandelion.*— The root of *Taraxacum officinale,* Compositæ. Temperate zone.

Preparations:

Extractum Taraxaci (U. S. P., B. P.).— Pilular. As pill excipient. 1 Gm. = 15 grs.

Fluidextractum Taraxaci (U. S. P., B. P.).— *Dose:* 8 c. c. = 2ʒ.

Elixir Taraxaci Compositum (N. F.).— With aromatics. As flavor.

Succus Taraxaci (B. P.).— *Dose:* 4 to 8 c. c. (1 to 2 drachms).

Xanthoxylum (U. S. P.).— *Prickly Ash.*— The bark of *X. americanum* and *X. Clava-Herculis,* Rutaceæ; North America. It contains berberin, and acts as a bitter.

The *fluidextract* is official (U. S. P.). *Dose:* 2 c. c. = 30 ♏.

Berberis (U. S. P.).— The rhizome and roots of *B. aquifolium* and other species, Berberidaceæ. North America. Berberin $C_{20}H_{17}NO_4$ (intensely yellow).

Fluidextr. Berberidis. (U. S. P.).— 2 c. c. = 30 ♏.

Nux Vomica.— See Index.

II. Astringent Bitters.

With these, tannin is a prominent ingredient, whilst volatile oils are present only in small quantity, if at all. The preparations can be mixed with water.

Cascarilla (B. P.).— The bark of *Croton Eluteria,* Euphorbiaceæ. Bahama. *Dose:* 0.6 to 2.0 Gm. (10 to 30 grains).

Infusum Cascarillæ (B. P.).— 5%. *Dose:* 15 to 30 c. c. (½ to 1 oz.).

Tinctura Cascarillæ (B. P.).— 20%. *Dose:* 2 to 4 c. c. (½ to 1 drachm).

Cinchona.— See Index.

***Condurango.**— The bark of *Marsdenia Condurango,* Asclepiadeæ. Ecuador. Said to have a specific effect in carcinoma and ulcer of the stomach.

Preparations:

**Fluidextractum Condurango.*— *Dose:* 1.0 to 1.5 c. c. (15 to 25 minims).

**Vinum Condurango.*— 1 : 10. *Dose:* 4 c. c. (1 drachm).

Serpentaria (U. S. P., B. P.).— *Virginia Snakeroot.*— The rhizome and roots of *Aristolochia Serpentaria* and of *A. reticulata,* Aristolochiaceæ. United States.

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* **Not official.**

Preparations:

Fluidextractum Serpentariæ (U. S. P.).—*Dose:* 1 c.c.=15 ♏.

Tinctura Serpenatariæ (U. S. P., B. P.).—20%. *Dose:* 4 c.c.=1ʒ.

Liquor Serpentariæ Concentratus (B. P.).—50%. *Dose:* 2 to 4 c.c. (½ to 1 drachm).

Cimicifuga (U. S. P., B. P.).—*Black Snakeroot, Black Cohosh.*—The rhizome and roots of *Cimicifuga racemosa,* Ranunculaceæ. North America.

Preparations (made with strong alcohol and not miscible with water):

Extractum Cimicifugæ (U. S. P.).—Powdered. *Dose:* 0.25 Gm.= 4 grs.

Fluidextractum Cimicifugæ (U. S.P., B. P.).—*Dose:* 1 c.c.=15 ♏.

Tinctura Cimicifugæ (U. S. P., 20%; B. P, 10%).—*Dose:* 4 c.c.= 1ʒ.

Cuspariæ Cortex (B. P.).—*Angostura Bark, Cusparia.*—The bark of *Cusparia febrifuga,* Rutaceæ. Tropical South America. *Dose:* 0.6 to 2.5 Gm. (10 to 40 grains).

III. Aromatic Bitters.

These contain both aromatic oils and bitter principles, but no tannin. Their alcoholic preparations cannot be mixed with water without turbidity (or filtering).

Calamus (U. S. P.).—*Sweet Flag.*—The rhizome of *Acorus Calamus,* Aroideæ. Europe and North America.

Preparations:

Fluidextractum Calami (U. S. P.).—*Dose:* 1 c.c.=15 ♏.

Aurantii Amari Cortex (U. S. P.) [*Aurantii Cortex Siccatus* and *Recens,* B. P.].—*Bitter Orange.*—The rind of the fruit of *Citrus vulgaris* (*Citrus Aurantium,* var. Bigaradia, B. P.), Rutaceæ. Cultivated in subtropical countries.

Preparations:

Fluidextractum Aurantii Amari (U. S. P.).—*Dose:* 1 c.c.=15 ♏.

Tinctura Aurantii Amari (U. S. P., B. P.).—20%. *Dose:* 4 c.c. =1ʒ.

Infusum Aurantii (B. P.).—5%. *Dose:* 15 to 30 c.c. (½ to 1 oz.).

Infusum Aurantii Compositum (B. P.) contains other aromatics. *Dose,* as the infusion; also enters into Syrupus Aromaticus, Syr. Aurantii, and Vin. Aurantii (B. P.).

* **Absinthium.**—*Wormwood.*—The leaves and tops of *Artemisia Absinthium,* Compositæ. Europe.

Preparations:

* *Oleum Absinthii.*—Prep. by distillation. *Dose:* 0.05 to 0.1 c.c. (1 to 2 drops).

* *Infusum Absinthii.*—1 : 16. *Dose:* 30 to 60 c.c. (ʒj to ij).

* *Absinthe.*—A liqueur consisting essentially of a solution of the oil in alcohol, of a strength of about 50%, with the addition of aromatics and coloring-matter. Ordinary amounts have effects analogous to those of alcohol, but if taken in excessive quantities, it induces mania and epileptiform conditions.

* **Achillea.**—*Yarrow.*—The herb of *Achillea millefolium,* Compositæ. Northern temperate zone. *Dose:* 2 to 4 Gm.

Humulus.—Also acts as bitter. For Materia Medica see Index.

* **Panax.**—*Ginseng.*—The root of *Panax quinquefolium,* Araliaceæ, very highly valued by the Chinese, belongs to this series. So do *other species* of Panax and Aralia.

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* Not official.

IV. Other "Bitters" Used in Domestic Medicine

are the following: Cnicus Arvensis, Æsculus glabra, Agrimonia Eupatoria, Plantago major, Scrophularia nodosa, Lappa officinalis, Adiantum pedatum, Coptis trifolia, Eupatorium purpureum, Fraxinus, Viburnum prunifolium, Sarracenia purpurea, Saxifraga Pennsylvanica, Pentstemon pubescens, Cynoglossum officinale, Asimina triloba, Menispermum Canadense, Gratiola virginica, Dipsacus sylvestris, Cephalanthus occidentalis, Ambrosia bidentata, Geum rivale, Lycopus Virginicus, Menyanthes trifolia, Polyporus officinalis, Prinos verticillata, Sabbatia campestris, Scutellaria latifolia, Simaruba officinalis, Marrubium vulgare, Berberis vulgaris, Boldoa fragrans, Chondrodendron tomentosum, Frasera Carolinensis.

These possess no advantage over the other Bitters.

V. Compound Bitters.

The taste and effect of bitters may be greatly enhanced by a proper blending. Indeed, these compound preparations almost always deserve the preference. The official mixtures have already been mentioned, viz.:

Tinctura Gentianæ Composita (U. S. P., B. P.).— See under Gentian.

Elixir Aromaticum (U. S. P.).— See Index.

Also the National Formulary:

Elixir Gentianæ (*Detannata*).— See Index.

To these may be added:

* *Tinctura Amara* (N. F.).— *Dose:* 4 to 8 c. c. (1 to 2 drachms).

* *Vinum Aurantii Compositum* (N. F.).— *Dose:* 5 to 15 c. c. (2 to 4 drachms).

VI. Aromatics, Carminatives, and Condiments.

These have been largely discussed in connection with other groups, especially under the aromatic flavors (Chapter VI) and organic irritants (Chapter XXIX), and may be consulted through the Index. The crude drugs are used as powders or infusions, 0.3 to 1.5 Gm. (5 to 25 grs.); the oils, 0.05 to 0.3 c. c. (1 to 5 ♏); the spirits or tinctures, 1. to 4. c. c. (30 to 60 ♏s).

The most important are:

Spir. Menthæ Pip.— 2 c. c. = 30 ♏.
Tinct. Zingiberis.— 2 c. c. = 30 ♏.
Tinct. Cardamomi Co.— 4 c. c. = 1 ʒ.
Pil. Asafœtidæ.— One pill.

The following drugs and their preparations may be used as carminatives (alphabetical arrangement):

Anethum (Dill).— Oleum.
Anisum (Anise).— Ol. Spir.
Asafœtida.— Tinc. Emuls. Pil.
Camphor.— Spir.
Capsicum.— Oleoresin, Tinct.
Cardamomum.— Tinct. and Tinct. Cardam. Co.
Carum (Caraway).— Oleum.
Caryophyllus (Cloves).— Oleum.
Cinnamomum.— Oleum. Spir. Tinct. Aqua. Pulvis Aromaticus. Fluidext. Arom.
Coriandrum.— Oleum.
Fœniculum (Fennel).— Oleum, Aqua.

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* Not official.

* *Galanga.*— Tuber of Alpinia officinorum, Scitamineæ, China.
Hedeoma (Pennyroyal).— Oleum.
* *Illicium* (Star-Anise).
* *Macis* (Mace).
Mentha Piperita (Peppermint).— Oleum. Spiritus.
Mentha Viridis (Spearmint).— Oleum. Spiritus.
Myristica (Nutmeg).— Oleum. Spiritus.
Myrrha.— Tinct.
Pimenta (Allspice).— Oleum.
Piper (Black Pepper).— Oleoresina. 30 mg. = ½ gr.
  Piperina, $C_{17}H_{19}NO_3$. Pale yellow crystals, insol. in water, sol. in 15 alcohol. *Dose:* 0.2 Gm. = 3 grs.
Sassafras.— Oleum.
Valeriana.— Tinct. and Tinct. Valerian. Ammon.
* *Zedoaria.*— Tuber of Curcuma Zedoaria, Scitamineæ, India.
Zingiber (Ginger).— Tinct. Fldext. Syrup. Oleoresin. Trochisc.

The following mixtures may be taken as types:

* *Mistura Magnesiæ et Asafœtidæ* (N. F.).— Magnesium Carbonate 5%, Tinct. Asafetida 7.5%, Tinct. Opium 1%. *Dose:* 2 to 8 c. c. (½ to 2 drachms).

* *Tinctura Capsici et Myrrhæ* (N. F.).— Capsicum 3%, Myrrh 12.5%. *Dose:* 0.6 to 2 c. c. (10 to 30 minims).

* *Chlorodyne* (for colic).— See Mist. Chlorof. et Cann Ind. Co., N. F., and Tinct. Chlorf. et Morph. Co., B. P., page 442.

(C) VEGETABLE CATHARTICS.

I. MANNER OF ACTION.

All vegetable irritants increase peristalsis when taken by mouth. However, those which have been classed as cutaneous irritants produce, when taken internally, a more marked effect upon the stomach, leading to vomiting; others act more specifically as carminatives; while still others tend to produce nephritis. These cannot be used in practice to affect peristalsis. The term "vegetable cathartic" is therefore restricted to those which irritate the intestine in a somewhat specific manner, with a much lesser action, if any, on skin, stomach, or kidneys.

The *reason for this peculiar limitation* of their irritant action to the intestinal canal depends upon their solubility or on certain phenomena of decomposition, both brought about by the alkaline reaction of the intestine.

Thus, castor oil and croton oil become active only when their fatty acids are liberated; croton oil contains some free acid and is therefore pustulant also on the skin. The group of "resins" are insoluble in water, but are decomposed and dissolved by alkalies.

The *bile* seems to be necessary for the activation of many of the resinous cathartics, the following being relatively or quite ineffective in its absence: gamboge, podophyllum, convolvulin, jalap, and scammonium (Buchheim and Stadelmann). The bile acts presumably by increasing the solubility. Rhubarb and senna are active in the absence of bile.

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* Not official.

A relatively mild irritation suffices for active catharsis. None of the vegetable cathartics are at all corrosive; and even toxic doses cause necrotic changes only as the result of excessive inflammation. The irritation is confined to the intestinal tract; the stronger cathartics escaping absorption, whilst the milder laxatives would scarcely be irritant even if absorbed. There is consequently no danger of nephritis.

The *inflammatory action* usually affects only the sensory endings which have to do with the setting-up of peristaltic impulses; but the action may extend deeper, and involve the muscles, etc. The result of the irritation is an *increased peristalsis,* with consequent hyperemia. If the irritation is violent, it also produces pain (colic or "griping").

The quickened peristalsis will cause expulsion of the intestinal contents before there is time for the absorption of liquid which normally occurs (especially from the large intestine). The stools are consequently soft to semifluid or liquid, according to the violence of the peristalsis.

It follows from this, that with moderate doses the fluid of the stools is not derived from the tissues; none the less, these become drier, since they are prevented from replacing the water lost by the urine and respiration.

The anthracene cathartics do not cause any secretion of fluid, even when large doses are given (Thiry, Brieger, Flemming); but large doses of the resinous cathartics cause the effusion of an inflammatory exudate into the intestine.

The anthracene and resinous cathartics also increase peristalsis if they are injected *subcutaneously* or intravenously; the resin-group is even more active by this channel. The action, however, is even then a local one, the constituents being excreted into the intestine. The cathartics are not administered in this manner, in practice, since the injection would be painfully irritant; the effects are also more easily controlled when the drugs are given by mouth. The isolated principles are not used, since the preparations of the crude drug produce a more certain and more extensive effect.

This is due to the fact that the principles are to some extent soluble and absorbable. They therefore irritate the stomach and often do not reach the intestinal canal. In the crude drugs they are protected by the presence of various colloid substances which prevent their irritant action and solution. For this reason, they reach the intestine without very much change, and since they remain here for a longer time, may develop their full action.

II. CLASSIFICATION.

The vegetable cathartics may be divided into three pharmacologic groups:

(*A*) *The Neutral Oils:*
These include *Croton Oil* and *Castor Oil.*

(*B*) *The Anthracene Derivatives.*— Emodin, cathartin, chrysarobin, and their acids.

These are the active principles of *Senna, Rhubarb, Rhamnus, Cascara Sagrada, Aloes.*

(*C*) *The Resinous Anhydrids:*

Jalapin, Scammonin, Elaterin, Podophyllin, Colocynthin, Gamboge, Euonymin.

(A) The Neutral Oils.— Croton Oil.— The active irritant principle of this is a fatty acid — *crotonoleic acid.* In the oil this exists mainly in the form of a glycerid, which is entirely inactive. Some, however, is free, so that the oil acts as a very strong irritant in any situation. On the skin it produces pustulation. In the intestine, the glycerid is split like any other fat, and the liberated acid may develop its action to the fullest degree, and is a most violent "drastic" purgative.

Oleum Tiglii (U. S. P.) [**Ol. Crotonis,** B. P.].—*Croton Oil.*—A fixed oil expressed from the seeds of *Croton tiglium,* Euphorbiaceæ. India and Philippines. Soluble in 60 parts of alcohol. Should be at least two years old. *Dose:* 0.015 to 0.12 c. c. (¼ to 2 drops), on a lump of sugar, slice of bread or of lemon (0.05 c. c. = 1 ♏, U. S. P.).

Linimentum Crotonis, B. P. (see p. 719.)

Castor Oil contains the glycerid of an analogous acid — *ricinolic acid;* the action of this is similar to that of crotonolic acid, but very much less violent. Since it does not exist at all in free form in the oil, this is perfectly bland and non-irritant to the skin or stomach.

In China it is used as an article of diet. The properties of Castor Oil were known to Herodotus; but Croton Seeds were first described in the middle of the sixteenth century.

Oleum Ricini (U. S. P., B. P.).—*Castor Oil.*—A fixed oil expressed from the seeds of *Ricinus communis,* Euphorbiaceæ. Cultivated. *Soluble* in an equal volume of alcohol. *Dose:* 8.0 to 60.0 c. c. (¼ to 2 oz.) (16 c. c. = 4 ʒ, U. S. P.).

The taste of castor oil is very nauseant to many persons. It is then best administered in the form of capsules.

Mistura Olei Ricini (B. P.).— A 40% emulsion flavored with Orange Flower and Cinnamon. *Dose:* 30 to 60 c. c. (1 to 2 oz.).

(B) Anthracene Derivatives:

The drugs of this group (Senna, Rhubarb, Cascara, Aloes) owe their activity to a series of substances, mostly glucosidal, which yield oxymethyl-anthraquinon by hydrolysis or by oxygenation in alkaline solution (Buchheim, Tschirch). It is these decomposition-products, and not the original constituents, which exert the cathartic action. The

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more important mother-substances are emodin, chrysophanic acid, chrysarobin, and in aloes, aloin. These are all derivatives of anthracene, $C_{14}H_{10}$. Chrysophanic acid and chrysarobin are entirely too irritant to be available as cathartics; in the drugs, their action is tempered by the presence of colloid extractives. Their decomposition occurs but slowly, so that these cathartics have a rather long latent period. The action never progresses to inflammation, which makes these drugs especially valuable when the purgative is to be taken habitually. Their action is mainly on the large intestine (Buchheim; Tappeiner and Brandl.)

Emodin is probably the most important of these principles. It is present in the amount of 0.8 to 1.% in senna; 2.6% in frangula; 0.6% in cascara; 0.8% in Cape aloes; and 1.5% in rhubarb. (Tschirch and Hiepe).

The drugs containing emodin *color the urine* yellowish brown when it is acid, reddish or violent when alkaline. It may be advisable to acquaint the patient with this fact.[1]

Senna (U. S. P.).—The leaflets of *Cassia acutifolia* [**Senna Alexandrina,** B. P.] (Alexandria Senna) or *Cassia augustifolia* [**Senna Indica,** B. P.] (India or Tinnevelly Senna), Leguminosæ. Eastern and Central Africa and India; cultivated. *Dose:* 5 to 15 Gm. (1 to 4 drachms) (4 Gm. = 1ʒ, U. S. P.). The leaflets of the Indian senna are much longer than those of the Alexandria variety.

Senna produces considerable griping. This may be almost abolished, without greatly reducing the strength of its action, by first exhausting it with strong alcohol.

Fluidextr. Sennæ (U. S. P.) is made in this manner. *Dose:* 2 c.c. = 30 ♏.

The stools occur about five to twelve hours after its administration.

The best preparation is an extemporaneous infusion. This must not be boiled very long, else the activity suffers.

The following are official:

Infusum [*Mistura,* B. P.] *Sennæ Compositum* (U. S. P., B. P.).—(*Black Draught.*) *Dose:* 120 c. c. = 4℥, U. S. P. An excellent preparation.

Contains per cent.: Senna 6, Manna 12, Magnes. Sulph. 12, Fennel 2.

Pulvis Glycyrrhizæ Compositus (U. S. P., B. P.).—*Compound Licorice Powder. Dose:* 2 to 8 Gm. (½ to 2 drachms) stirred in water (4 Gm. = 1ʒ, U. S. P.)

Contains per cent.: Senna 18, Sulphur 8, and Glycyrrhiza, Oil of Fennel, and Sugar.

Confectio Sennæ (U. S. P., B. P.).—Contains per cent.: Senna 10, Cassia Fistula 16, Tamarind, Prune, and Coriander. *Dose:* 4 to 8 Gm. (1 to 2 drachms) (4 Gm. = 60 grs., U. S. P.).

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[1] Exercise 13. Other *drugs which change the color of the urine* are: *Logwood* (Hematoxylon) does not color acid urine, but produces a reddish or violet color in alkaline urine. Santonin gives a yellow color to acid urine, with a yellow foam; if the urine is made alkaline it gives a very pronounced pink. Picric acid gives reddish-brown color in both acid and alkaline urine. The various coal-tar products give a brownish-black color. Methylen blue imparts a green color.

Syrupus Sennæ (U. S. P., B. P.).— Contains 25%. *Dose:* 4 c. c. = 1 ʒ (U. S. P.).

Infusum Sennæ (B. P.).— 10%; flavored with Ginger. *Dose:* 15 to 30 c. c. (½ to 1 oz.).

Liquor Sennæ Concentratus (B. P.).— 50%; contains Ginger. *Dose:* 2 to 4 c. c. (½ to 1 drachm).

Tinctura Sennæ Composita (B. P.).— 20%; with Aromatics. *Dose:* 2 to 4 c. c. (½ to 1 drachm).

**Species Laxantes* (N. F.) (*St. Germain Tea*).— Per cent.: 40 Senna, 10 Cream of Tartar; Elder flowers, Fennel, and Anise. *Dose:* 4 to 15 Gm. (1 to 4 drachms), as infusion.

Cassia Fistula (U. S. P.) [**Cassiæ Pulpa,** B. P.]— The fruit of *Cassia Fistula,* Leguminosæ. East India. *Dose:* 4 Gm. = 1 ʒ (U. S. P.).

Rheum (U. S. P.) [**Rhei Radix,** B. P.].—*Rhubarb.*— The rhizome of *Rheum officinale, palmatum,* and other undetermined species. Polygonaceæ. China; cultivated. (The species of Rhubarb cultivated in this country are devoid of cathartic properties.)

The Russian Rhubarb was exported *via* Russia, whilst the so-called Chinese or East India Rhubarb comes by water.

Records of the use of rhubarb in China date back to 2700 B.C.

The *principal constituents* are the cathartic principles: *Chrysophanic Acid,* $C_{15}H_{10}O_4$ (arises from chrysophan, $C_{27}H_{30}O_{14}$, when the root is boiled); *Emodin,* $C_{15}H_{10}O_5$; *Rhein,* $C_{15}H_{10}O_6$. (Note the close relations in the composition of these principles.) *Bitter Resins:* Erythroretin, Phæoretin, and Aporetin; *Rheotannic Acid; Rheumic Acid;* Calcium Oxalate, Starch, Sugar, Pectin, etc. (Tschirch and Heuberger, 1902).

Whilst the active principles show a general similarity with those of senna, certain of its constituents modify its action. The rheotannic acid tends to produce a secondary constipation. The bitter resins give it a stomachic action. On this account, and also because its taste is less disagreeable, it is preferred to senna for convalescents. It also produces less colic, and is generally milder. It acts in eight to ten hours.

Preparations:

Pulvis Rhei Compositus (U. S. P., B. P.).—(*Gregory's Powder.*)— Rhubarb, 25; Magnesia, 65; Ginger, 10. *Dose:* 2 Gm. = 30 grs., U. S. P.

Pilulæ Rhei Compositæ (U. S. P.).— Each contains: Rhubarb, 0.13 Gm. (2 grains); Aloes, 0.1 Gm.; Myrrh, 0.06 Gm.; and Oil of Peppermint. *Dose:* as stomachic, 1; as purgative, 2 to 4.

Pil. Rhei Composita (B. P.) contains the same ingredients. *Dose:* 0.25 to 0.5 Gm. (4 to 8 grains).

Extractum Rhei (U. S. P., B. P.).— By evaporation of fluidext. to pilular consistence. *Dose:* 0.25 Gm. = 4 grs., U. S. P.

Infusum Rhei (B. P.).— 5%. *Dose:* 15 to 30 c. c. (½ to 1 oz.).

Fluidextractum Rhei (U. S. P.).— Four-fifths alcohol. *Dose:* 1 to 4 c. c. (¼ to 1 drachm) (1 c. c. = 15 ♏, U. S. P.).

Liquor Rhei Concentratus (B. P.).— 50%. *Dose:* 1 to 4 c. c. (¼ to 1 drachm).

Tinctura Rhei (U. S. P.).— 20%. Cardamom, 4%. Glycerin and two-thirds alcohol. *Dose:* 4 c. c. = 1 ʒ, U. S. P.

Tinctura Rhei Aromatica (U. S. P., 20%; B. P., 10%).— Aromatics; one-half alcohol. *Dose:* 2 c. c. = 30 ♏, U. S. P.

Syrupus Rhei Aromaticus (U. S. P.).— Aromatic Tincture, 1; Syrup, 5½. *Dose:* 8 c. c. = 2 ʒ, U. S. P.

Mistura Rhei et Sodæ (U. S. P.).— Sod. bicarb., 3.5%; Fluidext

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* Not official.

Rhubarb, 1.5%; Fluidext. Ipecac, 0.3%; Sp. Peppermint, Glycerin, and Water. *Dose:* 4 c.c. = 1 ʒ, U. S. P.

Syrupus Rhei (U. S. P.).—Fluidext. Rhubarb, 10%; Pot. Carb., 1%; Cinnamon, Glycerin, and Syrup. [B. P., 5%; with coriander.] *Dose:* 8 c.c. = 2 ʒ, U. S. P.

Rhamnus Purshiana (U. S. P.) [**Cascara Sagrada,** B. P.].—*Cascara Sagrada.*—The bark of *Rhamnus Purshiana,* Rhamnaceæ. Pacific Coast of North America. Stored at least one year.

When the bark is first collected it is emetic. After two years' keeping this action is lost, and the cathartic quality is acquired. The active principles are: *Cascarin,* which is a cathartin or emodin principle; isoemedin, bitter resins, etc.; no chrysarobin or chrysophanic acid (Jowett, 1904: This author claims that emodin is not the main active constituent). The emetic action is said to be caused by a ferment.

Cascara is one of the best purgatives for continued administration. Its very disagreeable bitter taste is largely removed by treatment with alkalies, without materially impairing its action. This is done in the Aromatic Fluidextract. (This is sometimes called "tasteless," but is by no means so.)

Fluidextr. Rhamni Purshianæ (U. S. P.).—1 c.c. = 15 ♏.

Fluidext. Rhamn. Pursh. Aromaticum (U. S. P.).—Macerated with magnesium oxid. Aromatics. 1 c.c. = 15 ♏. The dose of the fluidextracts may be increased to 4 c.c (1 ʒ), if necessary.

Extract. Rhamn. Pursh. (U. S. P.).—Powdered. 1 Gm. = 4 Gms. of drug. *Dose:* 0.25 Gm. = 4 grs. (U. S. P.).

Frangula (U. S. P.).—*Buckthorn.* The bark of *Rhamnus Frangula.* Europe and Northern Asia. It corresponds closely with the preceding.

Preparations:

Fluidextractum Frangulæ (U. S. P.).—1 c.c. = 15 ♏.

Aloe (U. S. P., B. P.).—The inspissated juice of the leaves of *Aloe vera* (*Barbadoes or Curaçao Aloes,* Island of Barbadoes[1]); *Aloe Perryi* (*Socotrine Aloes,* Eastern Africa); *Aloe Chinensis,* and other species of Aloe. Liliaceæ. Numerous varieties are on the market, produced from different species and by different processes of manufacture. The Barbadoes and Socotrine are the most valuable. Aloe was used by the Greeks and probably by the Egyptians. The active principle, aloin, differs in the varieties.

Aloe is partly soluble in water, completely soluble in 5 parts of alcohol.

The action of aloes and aloin shows several peculiarities. In small doses they act as stomachics. Their cathartic action is greatly aided by bile, so that they may have very little effect in obstructive icterus. They occasion but little colic. On account of the intensely bitter taste, they are best given in the form of pills. They produce a comparatively strong congestion of the pelvic organs, and are therefore emmenagogue. This action forms a contraindication to their use in pregnancy, or when there are hemorrhoids. They are most useful in chronic constipation in middle life. The action is aided by alkalies and iron.

Dose: 0.03 to 0.06 Gm. (½ to 10 grs.). (0.25 Gm. = 4 grains, U.S.P.).

When injected hypodermically, aloin causes a tubular *nephritis.*[2] The anatomic lesions in rabbits have been investigated especially by Mürset (1885); they are practically the same in acute and chronic

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[1] Aloe is no longer exported from Barbadoes. This variety is probably grown in the island of St. Vincent. For the natural history of commercial aloes see Wilbert, 1903.

[2] Exercise 33.

poisoning, and consist mainly in degeneration of the epithelium of the convoluted tubules. This loses its striations and staining qualities, and the nuclei disappear. The glomerular epithelium is but slightly altered, and the glomerular vessels show no lesions. The urine may be increased or diminished and contains proteids, leucocytes, casts, crystals, and blood.

Preparations:

Aloe purificata.— Aloes softened by heating and addition of alcohol, strained and dried. This is the form which enters into most of the pills. *Dose* as for Aloes (0.25 Gm. = 4 grs., U. S. P.).

Extractum Aloes (U. S. P.) [——— *Barbadensis,* B. P.].— A dried watery extract. *Dose:* 0.03 to 0.2 Gm. (½ to 3 grains) (0.125 Gm. = 2 grs., U. S. P.).

Tinctura Aloes.— Licorice (U. S. P., 10%; B. P., 2.5%); ½ alcohol. *Dose:* 1 to 4 c.c. (¼ to 1 drachm) (2 c.c. = 30 ♏, U. S. P.).

Tinctura Aloes et Myrrhæ (U. S. P.).— 10% each, licorice, three-fourths alcohol. *Dose:* 2 c.c. = 30 ♏, U. S. P.

Decoctum Aloes Compositum (B. P.).— ½% of Extract of Aloes, with Myrrh, Pot. Carbonate, and Aromatics. *Dose:* 15 to 30 c.c. (½ to 1 oz.).

Aloes enters into a large number of pills, usually in combination with some carminative. Besides those enumerated here, into Pil. Cathart. Co., Rhei Co., etc. It is also the chief ingredient of very many proprietary pills.

In the following *U. S. Pills,* only the content of Aloes will be given; the *dose* is one to four:

Pilulæ Aloes: 0.13 Gm. (2 grains).

Pilulæ Aloes et Ferri: 0.07 (1 grain).

Pilulæ Aloes et Mastiches (Lady Webster's Dinner Pill): 0.13 (2 grains).

Pilulæ Aloes et Myrrhæ: 0.13 (2 grains).

The following *B. P. Pills* are official (the *Dose* is 0.25 to 0.5 Gm.— 4 to 8 grains):

Pilula Aloes Barbadensis: 50%.

Pilula Aloes et Ferri: 20% Aloes, 10% Iron Sulphate.

Pilula Aloes Socotrinæ: 50%.

Pil. Aloes et Asafœtidæ: 25% each.

Pil. Aloes et Myrrhæ: 45% Aloes, 25% Myrrh.

Aloinum (U. S. P., B. P.).— *Aloin* is usually Barbaloin, but sometimes Socaloin. It is soluble in 65 parts of water or 11 parts of alcohol. *Dose:* 0.03 to 0.12 Gm. (½ to 2 grains) (0.065 Gm. = 1 gr., U. S. P.).

The usual crystalline aloin itself is probably inactive, but is slowly converted in the intestine into the active amorphous modification. Its effect is less satisfactory than that of Aloes.

Pilulæ Laxativæ Compositæ (U. S. P.) (Aloin, Belladonna, and Strychnin Pills).— Each contains: Aloin, 13 mg. (⅕ gr.); Strychnin, 0.5 mg. ($^1/_{120}$ gr.); Extr. Belladonn., 8 mg. (⅛ gr.); Ipecac., 4 mg. ($^1/_{16}$ gr.). *Dose:* Two pills.

* **Purgatin** (Diacetyl ester of Anthrapurpurin).— A synthetic compound of the emodin group, with actions resembling aloin, has not yet been subjected to sufficient clinical tests. *Dose:* 0.5 to 1 Gm. (7 to 15 grains).

(C) Group of Anhydrids.— Although the constitution of these principles is not at all understood, their chemic re-

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* Not official.

actions, as well as their physiologic effects, show so many points of similarity as to cause them to be placed in one group.

The active principles are for the most part resinous (*i. e.*, soluble in alcohol, but slightly soluble in water), often glucosids, and on chemic manipulation (probably hydration) they yield acids. The latter are much less active.

It is characteristic of these principles that they are *not as effective when given pure* as when they are mixed with some extractive, as in the crude drugs and "resins" (alcoholic extracts precipitated by water), or as preparations of the crude drug. This is due, in some cases, to their being somewhat soluble, and therefore absorbed in the stomach.

All of the members of this group require the presence of bile, presumably to render them soluble. Their action seems to be largely peripheral, for it occurs after the section of the splanchnics and vagi.

The drugs of this series are generally *much more irritant* than the anthracene derivatives. They belong to the *drastic or hydragogue cathartics.* It is difficult to limit their action sufficiently to make them useful as aperients, and they are only employed when very active catharsis is essential. They should be avoided with children. The principal ones are the following:

Jalapa (U. S. P., B. P.).—*Jalap.*—The tuberous root of *Ipomœa Jalapa.* Convolvulaceæ. Eastern Mexico. *Active principles:* Convolvulin and Jalapin. Assayed for resin. *Dose:* 0.3 to 1 Gm. (5 to 15 grains) (1 Gm. = 15 grs., U. S. P.).

Jalap acts in about three hours. It is often given with calomel.

Preparations:

Resina Jalapæ (U. S. P., B. P.).—Extraction with alcohol and precipitation of the resin with water. *Dose:* 0.06 to 0.3 Gm. (1 to 5 grains) (0.125 Gm. = 2 grs., U. S. P.).

Pulvis Jalapæ Compositus (U. S. P., B. P.).—Jalap 1, Pot. Bitartrate 2. *Dose:* 1 to 4 Gm. (¼ to 1 drachm) (2 Gm. = 30 grs., U. S. P.).

Tinctura Jalapæ (B. P.).—20%. Three-fourths alcohol. *Dose:* 2 to 4 c. c. (½ to 1 drachm).

Scammonium (U. S. P., B. P.).—*Scammony.*—A gum-resinous exudation from the living root of *Convolvulus Scammonia,* Convolvulaceæ. Western Asia. *Active principle:* Jalapin. *Dose:* 0.3 to 1 Gm. (5 to 15 grains) (0.25 Gm. = 4 grs., U. S. P.).

Preparations:

Resina Scammonii (U. S. P., B. P.).—Extraction with alcohol and precipitation of the resin with water. *Dose:* 0.2 Gm. = 3 grs., U. S. P.

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Pilula Scammonii Composita (B. P.).— Contains Ginger. *Dose:* 0.25 to 0.5 Gm. (4 to 8 grains).

Pulvis Scammonii Compositus (B. P.).— Contains Ginger. *Dose:* 0.6 to 1.3 Gm. (10 to 20 grains).

Podophyllum (U. S. P., B. P.).—*May Apple, Mandrake.*[1]— The rhizome and roots of *Podophyllum peltatum,* Berberideæ. North America. *Active principles:* Podophyllotoxin and Picropodophyllin. *Dose:* 0.3 to 1.2 Gm. (5 to 20 grains) (0.5 Gm. = 7½ grs., U. S. P.).

The active principles do not exist in the fresh root, but develop on drying and storing; best after two years.

Preparations:

Fluidextractum Podophylli (U. S. P.).— Made with four-fifths alcohol. *Dose:* 0.3 to 1.2 c. c. (5 to 20 minims) (0.5 c. c. = 8 ♏, U. S. P.).

Resina Podophylli (U. S. P., B. P.).—(*Podophyllin.*)— By extraction with alcohol and precipitation of the resin by water. *Dose:* 0.008 to 0.03 Gm. (⅛ to ½ grain). (As laxative, 5 mg. = 1/10 gr., as purgative, 15 mg. = ¼ gr., U. S. P.)

Pilulæ Podophylli, Bellad. et Capsic (U. S. P.).— Each pill contains: Resin Podophyll., 16 mg. = ¼ gr.; Ext. Bellad., 8 mg. = ⅛ gr.; Capsicum, 32 mg. = ½ gr. *Dose:* One pill.

Colocynthis (U. S. P.) [**Colocynthidis Pulpa,** B. P.].—*Bitter Apple.*— The fruit of *Citrullus Colocynthis,* Cucurbitaceæ. Asia, Africa, Greece, and Spain. *Active principle:* Colocynthin. The decomposition product of this glucosid — colocynthein — is also active. *Dose:* 0.065 Gm. = 1 gr.

Preparations:

Extractum Colocynthidis (U. S. P.).— Made with one-half alcohol. Powdered. *Dose:* 0.03 to 0.1 Gm. (½ to 2 grains) (30 mg. = ½ gr.).

Extractum Colocynthidis Compositum (U. S. P., B. P.).— Contains Colocynth, Aloes, Scammony, Cardamom, and Soap. *Dose:* 0.3 to 1.0 Gm. (5 to 15 grains) (0.5 Gm. = 7½ grs.).

Pil. Colocynthidis Composita (B. P.).— Contains the same active ingredients as the Pulvis. *Dose:* 0.25 to 0.5 Gm. (4 to 8 grains).

Pilulæ Catharticæ Compositæ (U. S. P.).— Each pill contains:

	GRAMS.	GRAINS.
Compound Extr. Colocynth	0.08	1¼
Calomel	0.06	1
Extract Jalap	0.02	⅓
Gamboge	0.015	¼

Dose: One to four.

Pilulæ Catharticæ Vegetabiles (U. S. P.).— Each pill contains:

	GRAMS.	GRAINS.
Compound Extr. Colocynth	0.06	1
Extract of Hyoscyamus	0.03	½
Extract of Jalap	0.02	⅓
Extract of Leptandra	0.015	¼
Extract of Podophyllum	0.015	¼
Oil of Peppermint	0.008	⅛

Dose: One to four.

Elaterinum (U. S. P., B. P.).— A neutral principle obtained from *Elaterium* (B. P.), a substance deposited by the juice of the fruit of *Ecballium Elaterium* (Squirting Cucumber), Cucurbitaceæ. Western

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[1] The name "Mandrake" is also applied to Mandragora, which belongs to the atropin group.

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Asia, Northern Africa and Southern Europe; cultivated. *Dose:* 0.003 to 0.005 Gm. (1/20 to 1/12 grain) (5 mg. = 1/12 gr., U. S. P.).
Preparations.

Trituratio Elaterini (U. S. P.).—1 : 10. *Dose:* 0.03 to 0.06 Gm. (½ to 1 grain) (30 mg. = ½ gr., U. S. P.).

Pulvis Elaterini Compositus (B. P.).—1 : 40 in Sugar of Milk. *Dose:* 0.06 to 0.25 Gm. (1 to 4 grains).

* **Bryonia.**—The root of *Bryonia alba* and of *B. dioica*, Cucurbitaceæ. Central and Southern Europe. *Active principles:* The glucosids Bryonin and Bryonidin. *Dose:* 0.6 to 4.0 Gm. (10 to 60 grains).

Cambogia (U. S. P., B. P.).—*Gamboge.*—A gum resin obtained from *Garcinia Hanburii*, Guttiferæ. Anam, Camboja, and Siam. *Active principle:* Gambogic Acid. Since this is fairly soluble, even the gum-resin is irritant to the stomach, so that it should always be given in pill form. *Dose:* 0.06 to 0.3 Gm. (1 to 5 grains) (0.125 Gm. = 2 grs., U. S. P.).

Pilula Gambogiæ Composita (B. P.).—Contains Aloes. *Dose:* 0.25 to 0.5 Gm. (4 to 8 grains).

Leptandra (U. S. P.).—*Culver's Root.*—The rhizome and roots of *Veronica Virginica*. Scrophulariaceæ. United States. *Active principle:* The glucosid Leptandrin.
Preparations:

Extractum Leptandræ (U. S. P.).—Made with three-fourths alcohol. Powdered. *Dose:* 0.25 Gm. = 4 grs., U. S. P.

Fluidextractum Leptandræ (U. S. P.).—Made with three-fourths alcohol. *Dose:* 1 to 4 c. c. (¼ to 1 drachm) (1 c. c. = 15 ♏, U. S. P.).

* **Iris.**—*Blue Flag.* The rhizome and roots of *Iris versicolor*, Irideæ. North America. *Active principle* not well known. *Dose:* 1 Gm. = 15 grs.

Stillingia (U. S. P.).—*Queen's Root.*—The root of *St. sylvatica* Euphorbiaceæ, Southern United States. *Active principle:* pungent resin, fixed and volatile oils. Used mainly in domestic medicine, in purgative mixtures; also as nauseant and emetic. *Dose:* 2 Gm. = 30 grs., U. S. P.

Fluidextractum Stillingiae, (U. S. P.).—Diluted alcohol. *Dose:* 2 c. c. = 30 ♏., U. S. P.

* **Juglans.**—*Butternut.*—The root-bark of *J. cinerea*, Juglandaceæ. North America. To be collected in autumn. Used as *Extractum Juglandis* as a rather mild laxative, in *doses* of 1 to 2 Gm. (15 to 30 grains) of the extract.

(D) SUMMARY OF CATHARTICS.

Cathartics or *Evacuants* are drugs which cause an increase in peristalsis.

I. MANNER OF ACTION.

The intestines are to some extent under the control of the central nervous system; *e. g.*, a sudden fright may cause evacuation of the bowels; melancholia is frequently the cause of constipation. However, this central influence is quite exceptional, and cannot be utilized therapeutically, except in so far as regulation of the bowels by habit is concerned. All the remedial measures depend upon local actions.

Pharmacologically, these may be divided into: (*a*) Measures which produce peristalsis by *directly* stimulating the efferent nerve-muscle chain; (*b*) measures which produce peristalsis *reflexly* in virtue of an irritation, or by swelling the volume of the intestinal contents.

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* Not official.

The former (*a*) comprise the alkaloids physostigmin, pilocarpin, etc. They are not useful in practice.

II. CLASSIFICATION.

Before taking up the practically used cathartics in detail, it may be well to classify them according to their clinical characters; *i. e.*, mainly by the strength of their action.

Such a classification is by no means sharp, for the same drug may belong to different groups, according to the amount used, and according to other conditions. The classification is rendered still more complicated by the fact that different authors do not use the same nomenclature, but often apply the same term to very different actions.

The following table gives what is probably the most useful clinical classification:

1. Laxatives or Aperients: Those which increase peristalsis only moderately, producing somewhat more frequent stools, of almost normal consistency, and this without causing notable irritation. They are active in *doses* of 10 Gm. or over:

Fruits, Manna, Honey, etc.; mechanical means (massage, charcoal, electricity, etc.); Sulphur, Magnesia, Carminatives, Bland-Oils (Olive, Cotton-seed, Linseed, etc.).

(Small doses of Cascara, Senna, Castor Oil, Rhubarb, and Ipecac are also laxative.)

2. Purgatives: Those which increase peristalsis actively, causing frequent semi-fluid stools.

(A) Simple Purgatives: Active in *doses* of 0.2 to 1 Gm. These cause considerable colic and irritation:

Aloes, Rhubarb, Senna, Cascara, Castor Oil, Bile, Calomel, small doses of drastics.

(B) Saline Purgatives: Active in doses of about 10 Gm. Rather profuse, watery stools, with practically no irritation or griping:

Sulphate of Sodium or Magnesium, Sodium Phosphate, Magnesium Citrate, Potassium Bitartrate, Rochelle Salt, etc.

3. Drastics: Produce watery stools, with much irritation. Large doses are apt to set up an enteritis. Active in *doses* of less than 0.1 Gm.:

Elaterium, Colocynth, Jalap, Scammony, Gamboge, Podophyllin, Croton Oil, the stronger Mercurials, and Antimony Sulphid.

The drastics and salines are called *hydragogues,* since they remove much fluid.

4. Those which quicken peristalsis particularly in the duodenum remove bile from the intestine by lessening its reabsorption and constitute the clinical class of **cholagogues** (see below). This comprises Aloes, Rhubarb, Mercurials, Podophyllin, Euonymin, Sod. Salicylate or Phosphate, Acid. Nitrohydrochlor. Dilut., Bile.

III. LAXATIVE MEASURES.

This division includes those measures which increase the bulk of the intestinal contents; those which act as mechanical irritants; physical measures; enemata; sulphur and magnesia.

(A) Substances Used to Increase the Bulk of the Intestinal Contents:

Liquid: Water (direct or indirect). Oils.
Solids: Indigestible food or insoluble medicines.

Large quantities of pure **water** may be given for this purpose, but this will be more effective in the shape of *carbonated drinks*—soda-water, etc. *Lemonade* acts partly by its acid. These liquids are more effectual if taken *cold,* since cold in itself stimulates peristalsis. (Water should not be taken in the form of liquids containing tannin—such as tea or red wines.) Water may also be introduced in the form of *succulent vegetables* and fruits—apples, tomatoes, melons, etc.—which, however, act in part like other fruits, by their pectin, acid, etc.

The liquid in the intestines may be increased *indirectly* by preventing its absorption through the use of *salts.*

The bland, fatty **oils,** in quantities larger than can be digested, form very efficient laxatives. They can, however, only be taken by patients with good digestion.

The same holds of **indigestible food.**

Constipation is very often caused by deficiency in the indigestible portion of the diet. It is a mistake to suppose that a diet which is entirely digested and absorbed is the best. Animals, for example, are entirely unable to subsist on such food, and in feeding-experiments it is frequently necessary to add cellulose in the form of filter-paper to maintain them in good condition. The functionation of the intestine is necessary to the organism; perhaps in effecting the removal of bile and other toxic products formed in the body, as well as of the toxins generated in the intestine by bacteria.

Cases of constipation arising from this cause may, of course, be at once benefited by a change of the diet to one containing more indigestible material, such as many vegetables rich in cellulose. The desirable limit may readily be exceeded.

Of medicinal agents which act in this way, *Manna* may be mentioned.

Manna (U. S. P.).—A concrete saccharine exudation from *Fraxinus Ornus,* Oleaceæ. Mediterranean coast. The chief constituents are Mannit (90%), Glucose, Fraxin, Mucilage, Resin. *Dose:* 15 to 60 Gm. (½ to 2 ozs.) (16 Gm. = ½ ℥, U. S. P.) as infusion.

(B) This class borders closely on the **mechanical irritants,** since the distention of the bowels constitutes in itself a source of mechanical irritation. However, the irritation is increased when the indigestible particles are sharp or gritty, as the seeds of fruit (strawberries, figs, etc.) or as the husks of grain (oatmeal).

Fruits, fresh or stewed, are generally laxative. They act in part by the water which they contain; partly by the non-absorbable pectin substances which swell the bulk of the feces; partly by acid salts which exert a chemic irritation; partly by their sugar, which acts, by osmosis, like a saline cathartic.

Charcoal acts purely mechanically.

Carbo Ligni (U. S. P., B. P.).—*Wood Charcoal.*—Made by heating wood without access of air. *Dose:* 1 to 4 Gm. (15 to 60 grains) (1 Gm. = 15 grs., U. S. P.).

The absorbent character of charcoal makes it useful as an antidote to many poisons, and in fermentative dyspepsia.

Carbo Animalis (U. S. P.), *Animal Charcoal* (Bone-black), is used for decolorizing.

Carbo Animalis Purificatus (U. S. P.) has been exhausted with HCl, and may be used in acid liquids for the same purpose.

(C) Of **physical measures** which have a laxative effect may be mentioned *massage, moderate exercise,* all kinds of *cold baths,* or *electricity.*

The latter may be applied by laying a large electrode on the abdomen and connecting another to the rectal tube, through which salt solution is flowing into the intestine. In this way the stimulation covers the greatest area.

(D) Enemata (*clysters*) are injections into the rectum. Any distention of the rectum will set up *peristaltic contraction* in this organ, and stimulate reflexly even the higher portions of the intestine. Pure water will suffice for this, but the effect will, of course, be greater if some irritant is added.

To secure the maximum motor effect, the injection must be used cold, and in fairly large quantity: Adults a pint, quart, or more; children according to age (at a year, an ounce, and about ½ ounce more for each year). Water and bland oils are also often used by high injection.

The *irritants* which are most commonly used in clysters are: Soap, castor oil, or molasses, 1 : 8; salt, 1 : 16; turpentine, 1 : 20 (emulsified with egg-yolk).

Pure *Glycerin,* which is mildly irritant by withdrawing water from the tissues, is sometimes injected into the rectum, in *doses* of 3 to 6 Gm. (½ to 1½ teaspoonful). Peristalsis sets in in a few minutes. The injection is painless if there are no abrasions. It may also be given as:

Suppositoria Glycerini (U. S. P.).—Each contains 3 Gm. (45 grs.) made with sodium stearate.

Enemata have an *advantage* over cathartics taken by mouth, in that they may be made absolutely non-irritant, and may therefore be used in conditions in which the other cathartics are positively contraindicated. On the other hand, they soon lose their efficiency.

If the purpose of the enema be merely to *soften hardened scybala,* they would be used warm, in copious quantities, preferably with soap; or as decoctions of mucilaginous substances.

Enemata also have other uses: For *local effects* on the rectal mucous membrane (astringents, etc.); for the *removal of parasites* (see p. 746); and as a method of *introducing medicine and nourishment* (see p. 133).

The dose of medicines per rectum is generally about twice as much as by mouth.

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For local effects, the astringents are used in the same strength as on other mucous membranes (see p. 692). When the injection is to be retained, it must be small in amount, warm, and non-irritant. (The irritation may be diminished by the addition of boiled starch.)

IV. IRRITANT CATHARTICS.

Whilst the number of substances which may irritate the intestine is very great, those which can be employed in practice as cathartics are rather limited, for various reasons.

An ideal cathartic should produce profuse and soft, but not too numerous evacuations, without pain, tenesmus, or nausea, and without leaving any tendency to constipation.

Irritants which cause a marked *irritation of the stomach* are excluded altogether. This is one reason why the pure principles are not employed. As has been said, these are usually protected by colloids in the preparations made from crude drugs. The cathartics in ordinary use are so chosen that they cause little or no gastric disturbance in individuals with healthy digestion. However, when this is impaired, it may be necessary to administer them in "intestinal capsules" (see p. 68).

All those which have a fairly strong action cause considerable *colic* or *tenesmus.* This is the necessary accompaniment of a violent peristalsis, and if the latter is desired, the former must be taken into the bargain. All that the physician can do is to inform the patient that it is a sign that the medicine is doing its work. The griping may, however, be excessive, in which case it can be corrected by the addition of a carminative.

The tendency to *congestion of the pelvic organs* is also a necessary consequence of intestinal irritation. Where this is strongly contraindicated, the non-irritant salines, or enemata, must be used.

All irritant cathartics leave a *tendency to constipation,* which may become very annoying, especially when they are used habitually. This is seen especially with rhubarb, less with senna or cascara. It is not often serious, and rarely necessitates an increase in the dose.

The mercurial purgatives produce a tendency to *nephritis,* which contraindicates their continued use.

The intestinal irritants may be divided into mechanical, vegetable, and mineral. The first have been summarized on page 737.

The special uses of the various *vegetable cathartics* have been partly discussed in the preceding sections, and will receive further mention in the following.

Mineral Irritants:

Acids.— It will be remembered that free acids cannot be employed for this purpose, since they do not reach the intestine. Practically the only form is as Cream of Tartar, which acts largely as a saline.

Salines.— See page 540.

Sulphur merely softens the stools, and is therefore particularly useful in piles (see page 673).

Of metals, *mercury* is the only one which is useful. It is best given as calomel, together with a vegetable irritant, to insure its prompt expulsion (see page 683).

Several **alkaloids,** whilst not themselves cathartic, are often useful in this connection.

Belladonna and *Morphin,* especially the former, relieve spasm from overstimulation of the intestine, and are therefore useful in constipation as the result of intestinal spasm (lead colic). Belladonna also serves to regulate the irritant action of the vegetable cathartics, and in this way lessens griping (Aloin, Belladonna, and Strychnin (see p. 732) is quite a favorite preparation; the rôle of the *Strychnin* is not understood.)

V. ACTION OF DRUGS ON THE BILE.

The important functions of bile in digestion, absorption, and peristalsis would make it very desirable to dispose over a class of preparations which would influence bile-secretion. Starting from the observation that the stools after certain cathartics have a darker or greenish color, the older therapeutists referred this to an increased secretion of bile, and distinguished these substances as *cholagogues* — remedies which increase the flow of bile. When these were subjected to physiologic experimentation on animals with biliary fistulæ, the results were at first contradictory, owing to the fact that the flow of bile shows considerable variations naturally, and these observations did not extend over a sufficient time to eliminate this factor. Recent unobjectionable experiments have finally settled this question. According to these, the only true cholagogues, increasing both the volume of bile and the absolute quantity of bile-salts, are bile and salicylates, especially the former. (Pfaff and Balch).

For this purpose, dried ox-bile may be given, two pills containing 0.25 Gm. each, three times a day, preferably coated with salol.

Bile salts have a typical digitalis action on the heart.

The action of salicylates is quite small, and they must be used in doses of 5 Gm. per day.

Fel Bovis (U. S. P.).— *Ox-gall.*— The fresh bile of the ox.

Fel Bovis Purificatum (U. S. P., B. P.).— Ox-gall evaporated after addition of alcohol. *Dose:* 0.5 Gm. = 7½ grs., U. S. P.

The other drugs formerly classed as "cholagogues"— mercury salts, the saline and drastic purges — are simply active cathartics or antiseptics. The dark color of the stools is due to their carrying the *normal* quantity of bile through the intestine without giving time for the normal change of the bile pigment to the lighter fecal pigment; or to diminution of the bacterial action which causes this change.[1] Acids and alkalies are also not true cholagogues, (Levene, etc., 1904), although it is conceivable that they may cause, reflexly, an emptying of the gall-bladder.

(E) USE OF CATHARTICS.[1]

Cathartics are perhaps the most ancient method of internal medication, and were for a long time practically the only method. Even the Greeks used the same word, *φαρμακειν*, both for internal medication in general and for the use of cathartics in particular. The present English word *physic* is similarly applied.

1. Cathartics are still used in many different conditions; most frequently, however, in constipation, particularly **habitual constipation.**

The *consequences* of habitual constipation need not be gone into in this place. They arise mainly from the absorption of toxic products, the result of bacterial putrefactive processes going on in the intestine. These substances are by no means uniform, and many have never been isolated. Some are toxins, others ptomains of the muscarin series; H_2S is also poisonous; so is indol, the appearance of which in the urine is usually taken as an index to this intestinal putrefaction. Since the greater number of these products tend to increase peristalsis,

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[1] Exercise 31.

they are to some extent their own antidotes, and are perhaps even useful in normal individuals. They only become objectionable if their production exceeds the ordinary limits.

The first object in the treatment of habitual constipation is to *remove the cause,* if possible. This cause will very frequently be found in *faulty habits;* irregularity in going to stool, in time of eating or quality of food, insufficient exercise, etc. These must be corrected if they exist, and this will often contribute more to a cure than any drugs.

Another cause of constipation is *atony* of the intestinal or abdominal muscles, either congenital or acquired. In these cases resort should first be had to mechanical means — massage and electricity. If these mechanical means are not sufficient, or for any reason cannot be applied, the pharmacologic remedies are indicated. The latter are also to be used when the cause of the constipation lies in the *pain* from hemorrhoids, or the *pressure* from tumors, or pregnancy.

In *using cathartics* the rule should always be to *employ the mildest remedy* which will accomplish the result. One reason for this is that soft, not liquid, stools are desired; but, further, a "habit" is quite readily acquired, so that the intestines will require stronger and stronger stimuli, and the usual cathartics gradually lose their efficiency. If the treatment has been begun with mild measures, stronger ones are left for later use if necessary. The habitual use of very irritant cathartics is also quite apt to engender a chronic enteritis. This mistake of taking strong purgatives continually is one made only too frequently.

Perhaps the best cathartics in habitual constipation are those of the cathartin group — senna, cascara, rhubarb, or aloes. There is really no objection to the prolonged use of these mild cathartics.

Occasionally one encounters patients with just sufficient knowledge to lead them to think that the taking of purgatives is against nature, and therefore necessarily detrimental; and who will object very seriously to using them. While this reasoning is very sound when the intestines are normal, it cannot stand when anything is abnormal, as in the case of atony. An atonic condition of the intestine requires the habitual use of cathartics, just as an atonic condition of the ciliary muscle requires the use of glasses. Both are harmful in health, both are indicated in disease.

The *time of day* in which cathartics are to be given is determined by the length of time which they require to produce their action.

The vegetable cathartics or calomel require, with moderate doses, ten to twelve hours; larger doses, five hours; and the drastics may even act in three hours. The cathartic salts act more promptly — *i. e.,* in one to three hours.

The rapidity and the extent of the action are, however, modified by the condition of the patient. Larger doses are required in constipation than in health; the effect is more prompt if it is made to coincide with the usual time of defecation; etc.

It is therefore customary to give the vegetable cathartics, as also calomel, in the evening before going to bed, so that they will act in the morning. However, if the constipation is the cause of insomnia, as sometimes happens, it is better to give them in the morning. The cathartic salts are usually given in the morning, before breakfast.

2. Purgatives frequently lead to the arrest of **diarrheas.**

This might at first view appear paradoxical. But one need only remember that diarrhea is a conservative process intended to remove the irritant agent, and it will be plain that, unless excessive, the employment of a cathartic is simply a support of nature. One must also remember that peristaltic impulses always travel in a downward direction. The irritation caused by a mass of putrefying material may set up quite a violent peristalsis below this point, while the mass itself may be but little affected. A cathartic, on the other hand, starting peristalsis high in the intestine, will sweep out the mass and remove the materies morbi.

3. Cathartics are indicated in those infectious diseases in which the seat of the **infection** is **in the intestinal canal.** If the bacteria have not yet penetrated into the tissues, their expulsion may abort the infective process, or will in all cases diminish it. Cathartics are in this way "intestinal antiseptics."

4. Cathartics are employed **to remove poisons** — bacterial or chemic — both from the intestinal canal itself and from the body. They will be useful in preventing the further absorption of a toxic agent, as well as the reabsorption of such poisons as are excreted into the intestine.

5. A further indication for the use of cathartics is **to soften the stools.** This is required in diseases of the rectum, especially hemorrhoids; also to prevent any tendency to straining during stool (in aneurysm, or hernia, or tendency to apoplexy).

6. Another use is in **dropsical conditions** of all kinds, to remove water from the body. This also affords relief to the kidneys, so that cathartics may be useful in *nephritis.*

7. Irritant cathartics are of value in **congestions,** especially of the brain, through changing the distribution of the blood. Since they draw more blood to the abdomen, they lower the general blood-pressure.

8. Cathartics are also used **to lower temperature** in fever. This action is not sufficiently explained. They do not affect the normal temperature.

Contraindications.— There are several contraindications to the use of cathartics, especially to the stronger kinds. All inflammatory conditions of the abdominal organs (peritonitis, gastro-enteritis, etc.) preclude the administration of intestinal irritants. Pregnancy and menstruation are contraindications to the use of the stronger cathartics, since the hyperemia may lead to abortion or excessive menstrual flow. General debility, tendency to collapse, threatened intestinal hemorrhage, and toxic spasm of the intestine, are further contraindications.

Experience has established which of the cathartics best meet the *special indications.* In *habitual constipation,* where the object is to produce the least irritation possible, rhubarb, senna, and cascara sagrada or aloes are chosen. In *diarrhea,* those which produce large and watery stools with the minimum of irritation are preferred; *i. e.,* the saline cathartics or castor oil. *To soften the feces,* sulphur and enemata deserve preference. For the *removal of liquid* from the body, the best would be the saline cathartics with the addition of either senna or rhubarb. For the *removal of poisons* or of other toxic products from the alimentary canal, one would use the most active — the drastic purgatives.

(F) ANTHELMINTICS.[1]

Anthelmintics (*anti,* against; *helminthos,* worm) **are** remedies used against intestinal parasites.

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[1] Exercise 56.

I. GENERAL CONSIDERATIONS.

An active peristalsis will tend to remove intestinal parasites, as well as the other intestinal contents. Active cathartics are therefore necessarily *Vermifuges* — *i. e.*, drugs which expel parasites. But these parasites, when in good condition, are endowed with remarkable faculties of maintaining their position in the intestines — by traveling in the direction opposite to peristalsis, or by fixing themselves to the intestinal wall by means of suckers or hooks, or by their serrated margins, etc. It therefore becomes necessary to lower their vitality. This may be done to some extent by appropriate diet. But this is rarely sufficient, and it is generally necessary to employ drugs which will paralyze them — *Vermicides*. Since the latter necessarily present some danger to the host as well, it is desirable that they should be used in the smallest doses. For this reason it is well to give them their maximum efficiency by preceding them with a course of diet which lowers the resistance of the parasite without affecting the host. The vermicides but rarely kill the parasites; these usually recover if they remain in the intestine. It is therefore very necessary to follow the vermicide by an active cathartic, usually a drop of croton oil.

II. PRELIMINARY DIETARY MEASURES.

A limitation of the proteids of the diet is generally regarded as injurious to the parasite, but care must be taken not to carry this so far as to weaken the resistance of the patient. Carbohydrates may be allowed in any amount. Mechanical irritants — vegetables rich in fiber; the seeds of strawberries, blackberries, or figs; the husks of grain, etc. — are very useful. So are "sharp" articles of diet — condiments, especially those of the mustard group, strongly salted meat, etc. At the time when the vermicide is taken, the intestinal canal should be fairly empty, so that the parasite will not be protected by the contents. The remedies are therefore usually given before breakfast, and no food is taken for several hours after. This unfortunately increases the tendency to the absorption of the poison, and to the local irritation. Vomiting may occur and render a repetition of the whole cure necessary. It has been attempted to circumvent this difficulty by combining the principles with tannin, but this lessens their action. The best that can be done is to inclose them in gelatin capsules.

III. VERMICIDES.

The substances which are toxic to intestinal parasites are in general toxic to all forms of protoplasm. The class of intestinal antiseptics are all to some extent vermicidal, but can scarcely be introduced in sufficient amount to kill the parasites without injuring the host. Special qualities are necessary for this end: The remedy must be absorbed to the smallest possible extent, since its absorption would not only render it deleterious to the patient, but would also prevent its reaching the lower portions of the intestine and acting on the parasites found there. On the other hand, it must be capable of penetrating the resistant, often chitinous, covering of these worms. This combination can only be secured with *volatile* poisons, whose vapors permeate the intestinal canal and penetrate into the parasites before there is time for an extensive absorption. The latter is also retarded by the presence of fixed oils; and, accordingly, it will be found that the majority of vermicides are solutions in a fixed oil, of some volatile poison, essential oils or volatile alkaloids, etc. From this volatility of the active principles, it follows necessarily that these drugs are ***not very stable;*** the more so since these principles also undergo chemic changes very readily. This uncertain activity has thrown mistrust on the whole class of anthelmintics. The pharmaceutic extracts or isolated principles share this instability, although to a less degree.

Finally, it is more than probable that these parasites, as most other forms of life, show ***peculiar susceptibility*** to certain poisons. There is some hope that further research will bring forth specific vermicides. At present, the following data have been gathered from empirical observations:

The most efficient for *Tapeworms* are Male Fern (especially for Bothriocephalus); Pelletierin (especially for Tænia); and Kosotoxin; for *Round Worms,* Santonin and Spigelia. *Thread Worms* are treated most efficiently from the rectum by enemata. Aspidium is also said to be effective against *Anchylostoma.*

It may be well to mention that the vermicides are ***under no circumstances absolutely safe.*** They should never be given unless the parasites or their eggs are actually demonstrated in the feces. This is also the time when treatment offers the greatest chance of success.

(A) Vermicides for Tapeworm.

1. **Turpentine** (see p. 698) is used in domestic medicine in tablespoon doses. It is uncertain, and produces such violent irritation of the alimentary canal and kidneys that it is not to be advised. The same holds true of **Chloroform.** *Thymol, Salol, Naphthol,* etc., have not been subjected to sufficient trial to permit an estimate of their value.

2. **Pumpkin** or *Melon Seeds,* fresh or at least not over a year old, are eaten in half-ounce or ounce doses, on the day preceding the regular treatment. They are not sufficiently active themselves, but serve to support other measures. It is not known in what their action resides, but they contain a large amount of fat, with traces of volatile oil and resins. The fresh "milk" of the cocoanut is also said to be anthelmintic.

Pepo (U. S. P.).—***Pumpkin Seed.*** The seed of ***Cucurbita Pepo,*** Cucurbitaceæ; cultivated. 30 Gm. = 1 ℥. U. S. P.

3. **Aspidium** (U. S. P.) [*Filix Mas,* B. P.].—***Male Fern.***—The rhizome of *Dryopteris* (Aspidium) *Filix mas* and *D. marginalis,* Filices. North America, Northern Asia, and Europe. *Dose:* 4 Gm. = 60 grs., U. S. P.

The active ingredients are Filicic Acid, a volatile oil, and a fixed oil. All seem to be necessary, but the filicic acid is the most active. On keeping the drug, this passes readily into its anhydrid, Filicin, which is absolutely inactive. (Jacquet, 1904, claims as the most active constituent an amorphous acid, *filmaron,* discovered by Kraft. This is very unstable in solution, but keeps well when dry.) The official

Oleoresina Aspidii [*Extractum Filicis Liquidum,* B. P.], made by extraction with acetone and evaporation, seems the only rational preparation. *Dose:* 1.0 to 4.0 c. c. (¼ to 1 drachm; 2 Gm. = 30 grs., U. S. P.), preferably in capsules.

Overdoses cause especially nervous phenomena: General depression, coma, and convulsions, collapse, and sometimes death; there is also usually a gastroenteritis. Disturbances of vision are not uncommon. The nerve-fibers are degenerated. The chance of absorption is stated to be increased by the presence of an excess of fixed oil in the intestines, so that it is *contraindicated* to use castor oil as cathartic.

4. **Granatum** (U. S. P., B. P.).—*Pomegranate.*—The bark of the stem and root of *Punica Granatum,* Punicaceæ. Cultivated in subtropical countries. *Dose:* 2 Gm. = 30 grs., U. S. P., usually given as infusion.

The *active constituents* are two volatile alkaloids—Pelletierin (= Punicin) and Isopelletierin (= Granatonin). There are, further, two less active alkaloids—Methylpelletierin and Pseudopelletierin. The drug also contains a large proportion (20%) of a peculiar tannin—Punicotannic Acid.

Decoctum Granati Corticis (B. P.).—20%. *Dose:* 15 to 60 c. c. (½ to 2 ozs.). The large amount of tannin in this preparation is very irritant to the stomach, and frequently circumvents the purpose of the drug by causing vomiting. To avoid this, and also to give greater uniformity, the isolated principle has been introduced:

Pelletierinæ Tannas (U. S. P.).—The tannate of the mixed alkaloids. Yellow powder, sol. in 235 water, 126 alcohol. *Dose:* 0.25 Gm. = 4 grs., U. S. P., to 0.5 Gm. (7 grains).

Overdoses produce results similar to those of Filix mas, but less violent. Applied to the eye, it produces miosis, as does also arecolin.

5. **Cusso** (U. S. P., B. P.).—*Kousso, Brayera.*—The female inflorescence of *Hagenia Abyssinica,* Rosaceæ. Abyssinia. *Dose:* 10.0 to 20.0 Gm. (2½ to 5 drachms). (The male flowers are powerfully emetic, and therefore useless as vermicides.) (16 Gm. = ½ ℥, U. S. P.)

The *active principle* is given as Kosotoxin, a non-nitrogenous neutral principle; also resins (Coussin and Cosin) and volatile oils, which probably aid.

* **Kamala.**—*Rottlera.*—The glands and hairs from the fruit capsules of *Mallotus Philippinensis,* Euphorbiaceæ. India, China, and Philippines. *Dose:* 10 Gm. (2½ drachms). The active ingredient appears to be *Rottlerin.*

* **Areca.**—The fruit of *Areca Catechu,* Palmæ. Southern Asia. Contains vermicidal volatile alkaloid (Arecolin). Areca is only used in veterinary medicine.

(B) Vermicides for Round Worms (Ascaris lumbricoides).

All the remedies for Tapeworm are to some extent effective; and the same dietetic measures, as well as subsequent purge, are necessary.

Santonica (U. S. P.).—*Levant Wormseed.*—The unexpanded flowerheads of *Artemisia pauciflora,* Compositæ. Turkestan. *Dose:* to 4 Gm. (60 grs.). Now obsolete, since it has no advantage over its chief constituent:

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Santoninum (U. S. P., B. P.).—*Santonin.*—$C_{15}H_{18}O_3$. The anhydrid of santonic acid. Colorless crystals, odorless, little taste. Sol. in 5,300 water, 34 alcohol, sol. in alkalies. 0.065 Gm. = 1 gr. Best given in the form of:

Trochisci Santonini (U. S. P.).—Each 30 mg. = ½ grain. *Dose:* for children, 1 to 2 troches; for adults, to 5; administered in evening.

Trochisci Santonini (B. P.).—Each 1 grain. *Dose:* half the preceding.

The *action* of santonin is not well understood, but there is no doubt that it drives the ascarides into the lower intestine, from which they can be dislodged by cathartics, especially calomel.

The santonin itself is practically insoluble, but in the intestine it is converted into the soluble and absorbable santonin-sodium. This is excreted in the urine as a substance which gives to the liquid a lemon-yellow color when acid, carmine-red when alkaline.[1]

Doses as small as 0.1 Gm. may cause "yellow vision"—*i. e.,* white light has at first a violet, then a yellowish-green hue, and these colors tint the entire field of vision. (Exactly the same phenomenon is sometimes seen with amyl nitrite.) The power of seeing in dim light is also lessened. It has been demonstrated that these effects are peripheral, and the theory is advanced, based on some experimental data, that santonin impairs the reproduction of the visual purple and violet, which are at first used very rapidly. There is no truth in the statement that it discolors the media of the eye (Filehne, 1900).

Still larger doses have often led to *toxic symptoms.* These comprise headache, vertigo, weakness, somnolence, *convulsions,* fall of temperature, delirium, vomiting, and diarrhea (Binz, 1877; Harnack, 1901).

The treatment would be symptomatic: emetics, cathartics, chloroform inhalation against the convulsions, etc. Santonin has also been tried against *epilepsy,* with very little success.

The following are used only in domestic medicine:

Spigelia (U. S. P.).—*Pinkroot.*—The rhizome and roots of *Spigelia Marilandica,* Loganiaceæ. Southern United States. Said to contain a volatile oil, volatile alkaloid, and a bitter principle and resin.

Fluidextractum Spigeliæ (U. S. P.).—One-half alcohol. *Dose:* 2 to 8 c.c. (½ to 2 drachms) (4 c.c. = 1 ʒ, U. S. P.).

Chenopodium.—*American Wormseed.*—The fruit of *Chenopodium ambrosioides* (variety anthelminticum), Chenopodiaceæ. Naturalized in United States. *Dose:* 1.0 to 2.0 Gm. (15 to 30 grs.). The active principle is probably a volatile oil—

Oleum Chenopodii (U. S. P.).—*Dose:* 0.2 c.c. = 3 ♏, U. S. P.

Tanacetum.—See Index.

(C) Vermicides for Thread Worms (Oxyuris).

These are usually treated most efficiently by the rectal injection of various irritants. The rectum is first washed with injections of iron, tannin, or bitters (quassia), to limit the secretion of mucus, and is then irrigated with solutions or emulsions of salt (℥ss to pt.), aloes (ʒj to pt.), or turpentine (ʒij to pt.), etc. Mercury salts are sometimes used as injection or suppository, but are dangerous.

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[1] Exercise 14.

* Not official.

Study Materia Medica Lesson 17.

CHAPTER XXXI.

EMOLLIENTS AND DEMULCENTS.

EMOLLIENTS and Demulcents are drugs which soften, "relax," protect, and "soothe" the parts to which they are applied; in other words, drugs which lessen irritation. The term *emollient* is restricted more to those used on the skin, *demulcent* to those applied to mucous membranes. No very sharp distinction can be drawn between these, and many belong to both classes; but, as a rule, the fats are used as emollients, the gums as demulcents.

These substances lessen the action of all chemic, mechanical or bacterial irritants; diminishing pain, reflexes, catarrh, and all manifestations of irritation.[1] They also delay and diminish absorption, particularly from the stomach, but also from the intestine, subcutaneous tissue, etc. In this way they diminish the systemic effects of absorbable poisons, whilst they prolong their local actions.

The action of these drugs must be conceived as mechanical, since they are chemically indifferent, and since they do not exert any salt action, as they are either colloidal or insoluble. They may therefore be placed in intimate contact with cells, without causing irritation. By their viscid, adhesive character, they tend to form a protective covering to the surfaces to which they are applied, hindering the access of other irritants.

The oils will prevent the penetration of water-soluble substances, the gums that of fats and resins. Gums also lessen the effects of crystalloids, although they do not impede their diffusion. They produce this effect by increasing the viscidity of the solution, thereby interfering with its transportation (von Tappeiner, 1902).

On the other hand, oils and substances dissolved in them are *absorbed from the intact skin,* whilst watery solutions are not (unless the substance be volatile). Systemic effects may therefore be secured by inunction with medicated oils or salves (*e. g.,* Ung. Hydrarg). The absorption depends on the penetration of the oil into the sebaceous glands. This can be greatly increased by rubbing the salve *into* the skin. The deep penetration of the fats can be demonstrated histologically, by their presence in the lymph-channels.

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[1] Exercises 18C and 25.

The true fats are gradually oxidized and disappear. But the mineral oils — petrolatum, etc. — are practically incapable of oxidation, remain in the subcutaneous tissue for a long time, and, acting as foreign bodies, may prove a source of irritation. The animal and vegetable fats, therefore, deserve the preference when penetration is to be secured (Sobieranski, Juckuff, Meyer).

The persistence of the mineral fats in the subcutaneous tissue has been utilized for the *correction of deformities* (*e. g.*, of the nose), by injecting subcutaneously a mixture of paraffins melting at about 40° C.

The oily emollients and glycerin also penetrate into the squames of the stratum corneum, and *render the skin more pliable* and resistant to injurious agencies. They reinforce in this manner the natural fat of the skin and prevent roughness and "cracks" from wind, cold weather, sunburn, skin-diseases, etc. *Glycerin* resembles the ordinary fats very closely in its therapeutic uses; but it has a primary irritant action, due to osmosis.

If emollients are applied to open wounds or denuded surfaces, they serve the function of an artificial epidermis, furnishing a protection against injurious agents. The same result can be secured by covering the surface with a thin pellicle of an impermeable substance, as by applying *collodion* or *resinous tinctures,* and allowing the solvent to evaporate; or by applying *plasters* or bandages. The latter cannot be discussed in this place. The plasters differ from other fats mainly in their firmer consistency. On this account they are much more slowly absorbed, and can be applied for a longer time. However, their action also differs from that of plain ointments in being more irritant. This is due partly to their preventing entirely all evaporation from the skin, partly also to small quantities of volatile oils contained in the resins from which they are prepared. They are frequently useful as mild counterirritants for the relief of pain, absorption of swellings, hastening of abscess formation, etc. They are also employed for the conveyance of drugs which are intended to act purely locally, and to be absorbed very slowly, such as Belladonna, Aconite, Capsicum, etc.

Adhesive plaster acts purely mechanically. Poultices are also largely emollient.

Another class of substances, exerting a similar action, but physically very different, are the *dusting-powders*. These could be arranged into several classes. The simple powders are very fine ("impalpable"), indifferent, insoluble, non-irritant powders, such as talcum, chalk, starch, lycopodium, etc. They form a covering, just as do the fats, and are also used to prevent friction. They absorb secretions by capillary action, and are therefore drying. The metallic oxids and carbonates are in addition somewhat astringent. The absorbability of toxic metals, even when in the form of insoluble salts, must not be lost sight of, and lead compounds should be avoided altogether. Bismuth salts, except perhaps the subgallate, are also dangerous if applied to open surfaces. The zinc oxid and carbonate are entirely unobjectionable.

MATERIA MEDICA OF SIMPLE DUSTING POWDERS.

Talcum (U. S. P.).—A native hydrous magnesium silicate. Insol. in water and in dilute acids and alkalies.

Talcum Purificatum (U. S. P.).—Talc washed with dilute hydrochloric acid, is used for clarification.

Amylum (U. S. P.).—*Corn Starch.*—See Index.

Lycopodium (U. S. P.).—The spores of *Lycopodium clavatum* and other species, Lycopodiaceæ. Northern Hemisphere. Used only as dusting-powder.

Demulcents.—If soothing substances are applied to the mucous membrane of the respiratory or alimentary tract, their action must be conceived as parallel to that on the skin. But it must be remembered that this action is exerted only by that portion of the substance which adheres to the walls—not by that contained in the lumen. The gums, possessing a greater degree of "stickiness," are therefore more effective in these situations than the oils, and are the most useful *demulcents*.

The quality of drying, which renders them inapplicable to the skin, does not, of course, come into play here; whilst there is no thick stratum corneum to be softened, as by oils.

One sees a beautiful illustration of these facts in the natural lubricants of body-coverings. Whilst the skin is normally covered with a thin layer of oil, the membranes of the interior of the body are moistened with mucus, which is a typical gummy demulcent.

Gums, proteids and oils are useful against all forms of *irritant poisons,* whether introduced from without or formed in the body, as in faulty digestion. Milk or eggs are effective in the former case. Colloids will also *delay the absorption* of other substances, and this determines their use in pills, capsules, etc., as well as the advantages of extracts over alkaloids, etc., in certain cases. On the other hand, this interference with absorption is objectionable when the drug is given hypodermically. The demulcents are also useful in disguising or moderating the taste of disagreeable substances.

A good instance of their action in lessening irritation is the addition of boiled starch to *enemata,* to secure their retention. In *inflammation of the respiratory passages* — bronchitis, laryngitis, and pharyngitis — such a protection of the inflamed mucous membrane against the irritation of bacteria, air, and drying, must be of the greatest importance. Theoretically one would be inclined to think that their action would be limited to the upper portions of the respiratory tract; but clinical experience has shown that this is by no means the case, and that their action extends to remote bronchi. It would seem very unlikely that they would be excreted here, as has been claimed. Their effect must be either reflex, or else they must reach these parts by gradually flowing to them.

MATERIA MEDICA.

I. Bland Fatty Oils.

These oils are liquid, insoluble in water or glycerin, very sparingly in alcohol, freely in chloroform, ether, volatile oils, or fats.

They are used internally as foods and as laxatives (30 to 250 c. c. = 1 to 8 oz.). Full doses increase the quantity and fluidity of the bile, and are employed in cholelithiasis. *Olive oil* (tablespoonful, half an hour before meals) is used in hyperchlorhydria and in spastic constipation.

The fatty oils turn "rancid" on keeping, especially if they are exposed to air, light, and heat, and if they contain proteid impurities. Rancid oils are unfit for medicinal use.

Oleum Olivæ (U. S. P., B. P.).—*Olive Oil* (*Sweet Oil.*)—The fixed oil expressed from the ripe fruit of *Olea Europæa,* Oleaceæ. Cultivated in warm climates. The best oil for internal use. 30 c. c. = 1 ℥, U. S. P.

Oleum Amygdalæ Expressum (U. S. P., B. P.).—*Expressed Oil of Almond.*—A fixed oil expressed from Bitter or Sweet Almonds. 30 c. c. = 1 ℥, U. S. P.

Oleum Lini (U. S. P., B. P.).—*Linseed* (*Flaxseed*) *Oil.*—Expressed from Linseed. Disagreeable odor. 30 c. c. = 1 ℥ (U. S. P.). Employed mainly in liniments and in veterinary practice. "Boiled" oil should not be used.

Oleum Gossypii Seminis (U. S. P.).—*Cottonseed Oil.*—Expressed from the seeds of *Gossypium herbaceum* and other species, Malvaceæ.

Cultivated. On account of its cheapness, it is especially adapted for external use. It is often substituted for olive oil, but is greatly inferior for internal administration. It contains an irritant resin; and it cannot be readily emulsified or saponified, since the free fatty acids have been removed in the process of purification. 16 c.c. = ½ ℥, U. S. P.

Oleum Adipis (U. S. P.).—*Lard Oil.*—The liquid portion of lard. Many other oils may also be used.

II. Other Liquid Emollients.

Glycerinum (U. S. P., B. P.).—*Glycerin, Glycerol.*—($C_3H_5(OH)_3$.)—A thick, colorless liquid, of a sweetish taste, obtained by the decomposition of fats or fatty oils. Specific gravity, 1.240. Soluble in water or alcohol, insoluble in ether, chloroform, or oils. 4 c.c. = 1 ʒ, U. S. P.

Used locally, glycerin acts at first as an irritant, by abstracting water. This causes smarting in wounds.[1] It is utilized for catharsis, the glycerin being administered as enema (4 to 8 c.c. = 1 to 2 ʒ, undiluted), or as the official suppository. The irritant action is soon replaced by a soothing, demulcent or emollient, effect; glycerin being applicable to either skin or mucous membranes. When taken internally, it is readily absorbed and oxidized, serving as a source of energy; but it is scarcely a useful food. Its sweet taste has caused its use as a substitute for sugar in diabetes; but it is rather disagreeable to many persons. An important use of glycerin is as a pharmaceutic solvent and preservative.

Toxic Effects.—These have never been reported in man, but they occur in animals when large doses are given, by any channel. The symptoms are convulsant and paralytic, probably through a direct action of glycerin on the central nervous system. The blood-corpuscles are laked, especially if the glycerin is injected hypodermically. This is probably an osmotic effect, the glycerin remaining for a time unabsorbed, and in high concentration at the place of injection; and the corpuscles being laked during their passage through this area (Filehne).

On muscle-nerve preparations, glycerin acts similarly to veratrin (page 326).

Preparations: Glyceritum Amyli.—Suppositoria Glycerini.

Acidum Oleicum (U. S. P., B. P.).—*Oleic Acid.*—$H.C_{18}H_{33}O_2$. A yellowish or brownish oily liquid, insoluble in water, soluble in alcohol. Usually quite impure, containing other fatty acids. Used principally as solvent for medicines intended to be absorbed from the skin.

Petrolatum Liquidum (U. S. P.) [*Paraffinum Liquidum,* B. P.].—A mixture of hydrocarbons, chiefly of the marsh-gas series, obtained from petroleum, and purified until it has the required color (Fuscum, Flavum, Album, Albissimum, etc.). The official is almost colorless.

III. Semi-Solid Fats.

These possess the character of the fatty oils, except that they are soft solids at ordinary temperature.

Oleum Theobromatis (U. S. P., B. P.).—*Cacao-butter.*—A solid fat expressed from the seed of *Theobroma cacao,* Sterculiaceæ. Central and South America. Used mainly for making suppositories.

Study Materia Medica Lesson 52.

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[1] Roth has shown (with Cataplasma Kaolini), that glycerin does not abstract water from the *intact* skin; because of the impermeability of the stratum corneum.

Not to be confused with

* *Oleum Cocos.*—*Cocos-oil.*—The expressed oil of the cocoanut, the fruit of *Cocos nucifera,* Palmæ, Tropics. It is a whitish fat, soluble in alcohol, used especially in soap-making.

Sevum.—*Suet* (U. S. P., B. P.).—*Mutton Suet.*—The internal fat of the abdomen of the Sheep (*Ovis aries*), purified by melting and straining.

Adeps (U. S. P., B. P.).—*Lard.*—The internal fat of the abdomen of the pig (*Sus scrofa*). Other animals also yield fats which are popularly supposed to have special advantages—dog fat, goose grease, etc. There appears to be no reason for preferring them to the more easily obtainable lard.

Animal fats become rancid quite rapidly. Hence all ointments are directed to be prepared from:

Adeps Benzoinatus (U. S. P., B. P.).—Made by digesting lard with gum benzoin. In this process it takes up a certain amount of the latter, and acquires the antiseptic and stimulant properties of balsams, besides increasing its own keeping qualities.

* *Butyrum, Butter,* is sometimes used as an ointment basis. Since it can not be salted for this purpose, it keeps very poorly.

Adeps Lanæ (U. S. P., B. P.).—The purified fat of the wool of sheep, freed from water. Insoluble in, but miscible with, large quantities of water. Used for the administration of watery solutions in ointment form.

Adeps Lanæ Hydrosus (U. S. P., B. P.).—(*Lanolin.*)—The above, mixed with 30% of water. This is the form commonly used.

Wool-fat possesses a number of advantages as an ointment. It does not readily become rancid; it is absorbed with the greatest ease; and it is miscible with twice its weight of water. It consists mainly of cholesterins, together with some fatty acids.

IV. Soft Mineral Fats.

Petrolatum (U. S. P.) [*Paraffinum Molle,* B. P.].—*Petrolatum* (Vaselin).—A mixture of hydrocarbons obtained from Petroleum, melting between 45 and 48° C. (113 and 118.4° F.). Yellow color.

Petrolatum Album (U. S. P.).—The preceding product, rendered colorless (white).

* *Petrolatum Saponatum.*—Petrolatum, rendered more absorbable by emulsification with ammonium oleate.

V. Substances of a Waxy Consistency.

These are used to increase the solidity of ointments (as in cerates).

Cetaceum (U. S. P., B. P.).—*Spermaceti.*—A solid fatty substance obtained from the sperm whale (Physeter macrocephalus). It consists mainly of a combination of Cetylic Alcohol with Palmitic Acid. Melts at 45 to 50° C.

Acidum Stearicum (U. S. P.).—*Stearic Acid.*—$H.C_{18}H_{35}O_2$. Usually more or less impure; obtained by decomposing tallow. The commercial acid melts at 56° C. Sol. in 16.6 alcohol.

Cera Flava (U. S. P., B. P.).—*Yellow Beeswax.*—Melts at 62° to 64° C.

Cera Alba (U. S. P., B. P.).—*Bleached Beeswax.*—Melts at 64 to 65° C. Wax is but sparingly sol. in alcohol, sol. in ether, chloroform, and oils.

Paraffinum (U. S. P.) [*Paraffinum Durum,* B. P.].—*Paraffin.*—A white waxy solid, a mixture of solid hydrocarbons obtained from Petroleum. The melting-point lies between 51.6 — 57.2° C. Insol. in alcohol, sol. in benzin, ether, fats, etc.

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* Not official.

VI. Resins.

These usually contain some essential oils, and therefore act as mild dermal irritants. They are used in cerates and plasters.

Resina (U. S. P., B. P.).— *Rosin, Colophony.*— The residue left after distilling the volatile oil from Turpentine (see Index).

Pix Burgundica (B. P.).— *Burgundy Pitch.*— The prepared black resinous exudation of *Abies excelsa,* Coniferæ. Europe.

Elastica (U. S. P.) [*Caoutchouc,* B. P.].— *India-rubber, Caoutchouc* (Para Rubber).— The prepared juice of various species of *Hevea,* Euphorbiaceæ. Tropical countries. Soluble in Chloroform, Carbon Disulphid, Turpentine, Petroleum Ether, and Benzol. Swells in ether without dissolving. Consists mainly of polymers of terpene ($C_{10}H_{16}$). Combined with 3 to 10% of sulphur by heating, it gives *vulcanised rubber;* with 20 to 35%, *ebonite, hard rubber.*

Many other tropical plants, belonging especially to the families Euphorbiaceæ, Artocarpeæ, and Apocyneæ, also serve as sources of "rubber." This is contained in the milk-juice to the extent of 17 to 32%. It is separated from this juice by coagulating it through ferments or other means.

* *Gutta-percha.*— The concrete juice of *Dichopsis gutta* and other trees of the same order, Sapotaceæ. South America. Properties are similar to those of Rubber.

VII. Compound Emollient Ointments and Ointment Bases.

Unguentum (U. S. P.).— Lard 80, White Wax 20.

Unguentum Aquæ Rosæ (U. S. P., B. P.).— (Cold Cream.)— Spermaceti, White Wax, Expressed Oil of Almond, Rose Water, and Sodium Borate.

Unguentum Cetacei (B. P.).— Rosin, Yellow Wax.

* *Resorbin.*— An emulsion of Almond Oil, said to be very readily absorbed.

Glyceritum Amyli (U. S. P., B. P.).—Starch 10, Water 10, Glycerin 80.

Ceratum (U. S. P.).— White Wax, White Petrolatum. Benz. Lard.

Ceratum Resinæ (U. S. P.).—Rosin, Yellow Wax, Lard.

Ceratum Resinæ Comp. (U. S. P.).— Rosin, Yellow Wax, Suet, Turpentine, Linseed Oil.

VIII. Official Plasters.

Emplastrum Adhesivum (U. S. P.).— Rubber, petrolatum, lead plaster.

Empl. Ammoniari cum Hydrargyro (B. P.).

Empl. Belladonnæ (U. S. P., B. P.).—Extract Belladonna, adhesive plaster. 0.38 to 0.42% alkaloids.

Empl. Calefaciens (B. P.).— 8% Cantharides.

Empl. Cantharidis (B. P.).— 35%. The cerate is substituted in the U. S. (see Index).

Empl. Capsici (U. S. P.).— 0.25 Gm. of oleoresin per 15 cm. square; adhesive plaster.

Empl. Hydrargyri (U. S. P., B. P.).— 30% Hg; hydrous wool-fat, lead plaster.

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* Not official.

Empl. Menthol (B. P.).— 15%.

* *Empl. Ichthyocollæ.— Court Plaster.*— Made from

* *Ichthyocolla.— Isinglass.*— The swimming bladder of *Acipenser Huso* and other species, Sturiones. Caspian and Black Seas. Contains 98% of Gelatin.

Empl. Opii (U. S. P., B. P.).— 6% Extr. Opii, adhesive plaster.

Empl. Picis Burgundicæ (B. P.).

Empl. Plumbi (U. S. P., B. P.).— Lead or Diachylon Plaster (see Index).

Empl. Plumbi Iodidi (B. P.).— 10%.

Empl. Resinæ (B. P.).— *Adhesive Plaster.*— Rosin, lead plaster, yellow wax.

Empl. Saponis (U. S. P., B. P.).— Soap 10%, lead plaster.

IX. Demulcents: Oily Seeds.

These contain gum, oil, and starch. When rubbed with water, they form natural emulsions, which serve especially as emollients. For internal use they are taken as decoctions; *dose* ad libitum.

Amygdala Dulcis (U. S. P., B. P.).— *Sweet Almond.*— The seed of *Prunus Amygdalus* var. *dulcis*, Rosaceæ. Cultivated.

Emulsum Amygdalæ (U. S. P., 6 : 100; B. P., 12 : 100).— 120 c.c. = 4 ℥.

Pulvis Amygd. Compositus (B. P.) contains Acacia and Sugar.

* *Cydonium.— Quince Seed.*— The seed of *Cydonia Vulgaris*, Rosaceæ. Cultivated.

Linum (U. S. P., B. P.).— *Linseed, Flaxseed,* and *Linum Contusum* (B. P.), Crushed Linseed.— The seed of *Linum usitatissimum*, Lineæ. Cultivated.

Linseed is sometimes given as decoction in bronchitis. Its principal use, however, is in poultices (see Index).

An aseptic substitute is furnished by:

Cataplasma Kaolini (U. S. P.).— Essentially a thick mass of clay and glycerin (37.5%, with the addition of boric acid (4.5%), thymol, methyl salicylate, and oil of peppermint. This is spread in a thick layer on the surface, and left in place for 12 to 48 hours. It is more effective if applied hot.

Kaolinum (U. S. P.).—(*China Clay.*)— A native aluminum silicate, consisting chiefly of $H_2Al_2Si_2O_8 + 8\,H_2O$. A white powder.

Hemp seed and rape seed are also demulcent.

Seeds and tubers rich in starch may be used as demulcents in the form of decoction. They are enumerated under nutrients.

X. Gums.

(Gums are insoluble in alcohol! See page 23.)

Acacia (U. S. P.) [*Acaciæ Gummi*, B. P.].— *Gum-Arabic.* A gummy exudation from Acacia Senegal and other species, Leguminosæ. Northern Africa.

Acacias derived from other species have similar characters and uses.

Acacia is insoluble in alcohol, slowly but completely soluble in 2 parts of water, to a thick, mucilaginous, insipid liquid. This shows an acid reaction to litmus, and is precipitated by alcohol, borax, or metallic salts.

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Preparations:

Mucilago Acaciæ (U. S. P., B. P.).— A 34% solution, made by dissolving acacia in equal volumes of water and lime water (U. S. P.) [1½ parts, B. P.]. Used in many pharmaceutic preparations as emulsifier, excipient, etc.

Syrupus Acaciæ (U. S. P.).— 10%.

Tragacantha (U. S. P., B. P.).— *Tragacanth.*— A gummy exudation from *Astragalus gummifer* and other species, Leguminosæ. Western Asia. Swells to a gelatinous mass in water, without dissolving.

Mucilago Tragacanthæ (U. S. P., B. P.).— 6%. 16 c. c. = 4ʒ.

Glycerinum Tragacanthæ and *Pulvis Tragacanthæ Compositus* (B. P.).

XI. Demulcent Herbs and Other Demulcents.

All these can be taken in decoction, ad libitum. They contain mucilage as their most important ingredient.

Althæa (U. S. P.).— *Marshmallow.*— The root of *Althæa officinalis,* Malvaceæ. Cultivated.

Ulmus (U. S. P.).— *Slippery Elm Bark.*— The inner bark of *Ulmus fulva,* Urticaceæ. North America.

Mucilago Ulmi (U. S. P.).— 6% infusion.

Glycyrrhiza (U. S. P., B. P.).— *Licorice Root.*— See Index. As demulcent, best as * *Syrupus Glycyrrhizæ.*

Sassafras Medulla (U. S. P.).— *Sassafras Pith.*— The pith of *Sassafras variifolium,* Laurineæ. North America.

Mucilago Sassafras Medullæ.— 2%. Is not precipitated by alcohol.

* *Cetraria.*— *Iceland Moss.*— A lichen, Cetraria islandica. Iceland and Norway. Also contains a bitter principle, which can be extracted by cold water. Boiled with water after previous maceration with cold water, it yields a jelly (Decoctum Cetrariæ, 5%).

Chondrus (U. S. P.).— *Irish Moss* (Carrageen).— The seaweeds Chondrus crispus and Gigartina mammillosa. Iceland and North America. Yields jelly with boiling water.

Gelatinum (U. S. P., B. P.).— An air-dried product of the action of boiling water on gelatinous tissue. Soluble in hot water. Solutions of 2% and above solidify on cooling. Insoluble in alcohol. Also precipitated by carbolic acid; not by dilute solutions of metallic salts.

Gelatinum Glycerinatum (U. S. P.) is employed for making bougies, etc.

XII. Mechanical Protectives.

Certain substances which are used for this purpose may be mentioned in this place:

Collodium and Collodium Flexile (U. S. P., B. P.).— See Index. Ethereal solution of gun-cotton, leaving a protective film on evaporation. Used for dressing small wounds, etc.

Gossypium Purificatum (U. S. P.).— *Gossypium* (B. P.).— *Absorbent Cotton.*— The hairs of the seed of G. herbaceum and other species (Maloaceæ); cultivated. Freed from adherent impurities and from fat (so as to make it absorbent) and often sterilized. Consists of almost pure cellulose ($C_6H_{10}O_5$). Used in bandaging, etc., either as such, or as gauze (Tela, Carbasus), lint (lintum), etc., or impregnated with antiseptics, astringents, etc. *Wood-Wool* (chemically treated wood-fiber) has been introduced as a cheaper substitute.

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* Not official.

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Calcii Sulphas Exsiccatus (U. S. P.)—*Plaster of Paris,* Burnt Gypsum.—A fine white powder, which sets into a stone-like mass when mixed with half its weight of water. Used in bandaging. The "setting" takes place in 15 to 20 minutes. It may be delayed to an hour by the addition of 5% of glycerin, or hastened by the addition of sodium silicate. Plaster of Paris must be kept dry.

**Liquor Sodii Silicatis* (*Waterglass*).—A colorless syrupy liquid, of alkaline properties, but not corrosive. Contains about 20% of sodium silicate. Forms a solid glassy mass on exposure. Used in bandaging.

(Sodium silicate, given by the mouth or skin, acts like a typical mild alkali without showing any specific features. It is readily absorbed from the alimentary canal, and excreted by the urine. Injected intravenously it causes agglutination of blood corpuscles, and consequently intravascular clotting. Silicates are normally present in all tissues, but in very small amount) (Siegfried, 1901).

* Not official.

CHAPTER XXXII.

DRUGS ACTING UPON NUTRITION.

(A) DIGESTIVE FERMENTS.[1]

Ferments are substances which act by catalysis, *i. e.,* which accelerate in a specific manner slow chemic processes, in which they do not themselves take part. They act therefore in infinitely small proportion, and are not used up in the process. Ferments are classed as organized (such as yeast and bacteria) and unorganized. The latter class—also called *enzymes*—is the only one employed in therapeutics. It is very probable that the fermentations caused by cells are also in reality due to enzymes.

Nothing is definitely known concerning the *chemic nature of ferments,* or the manner in which they produce their actions. They have never been isolated in pure condition (the *commercial preparations* are quite impure). The analogous phenomena exhibited by colloid metals (see Index) incline to the view that the property is connected with the colloid nature of the ferments, presumably with the surface action of the aggregate particles. The action of ferments is *hindered by many poisons,* especially by the antiseptics, quinin, cyanids, fluorids. The comparative retarding effect is not the same for all ferments.[2]

When several proteolytic ferments are put in action at the same time, they often *destroy each other:* pepsin and trypsin digest each other; rennin, invertin, and emulsin do not seem to be affected by them; diastase is not harmed by invertin and trypsin, but is weakened by pepsin.

It is therefore *irrational to give by the mouth any ferment which is intended to act in the intestine,* unless it is administered in salol or glutol capsules.

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[1] The term "fermentation" is derived from fermentum, leaven; and this probably from fervere, to boil. It was originally applied to all effervescence.

[2] Exercise 19.

When the importance of ferments (enzymes) in digestion was recognized, the thought lay near at hand that they would be useful in many kinds of digestive disorders. However, much skepticism has arisen in recent years as to the benefits claimed as the result of their internal administration. Gastric digestion alone could theoretically be aided by ferments; and physiologists have long since demonstrated that gastric digestion is relatively unimportant. The symptoms of dyspepsia are rather due to irritation than to deficient digestion. And whilst there is no doubt but that the secretion of pepsin may be deficient in certain conditions, it is by no means proved that this is the case in the diseases in which such deficiency is ordinarily assumed. The benefits ascribed to pepsin should perhaps in many cases be credited to the other remedies which are joined to it. However, there can be no doubt that pepsin itself is beneficial in certain cases; and as its administration is neither dangerous nor unpleasant, it may be tried. When the gastric juice is deficient in *acid,* the activity of pepsin will be greatly diminished. The administration of acid by mouth will not always remedy this condition, since it may be too quickly absorbed. In this case *Papain* may be preferred, since it acts in all media. Unfortunately, the commercial preparations of this ferment differ very greatly in their value, and often do not possess any digestive property. No results whatsoever can be looked for from the administration of the pancreatic ferments.

Whilst the usefulness of ferments on internal administration is therefore a very limited one, the case is quite different with *in vitro* digestion. They are of the greatest value in the *preparation of predigested food* (see index).

Another use to which the proteolytic ferments may be put is the *solution of croupous or diphtheritic membranes* by local application.

I. Proteolytic Ferments.

Pepsinum (U. S. P., B. P.).—*Pepsin.*—Obtained from the mucous membrane of the stomach of the pig (or sheep or calf, B. P.). Capable of digesting not less than 3,000 parts of coagulated egg-albumen (U. S. P.) [2,500 parts, B. P.] when the test is made according to the official directions.

Various processes are used in its manufacture. The product may be in powder or scales. It is soluble in water, insoluble in alcohol, etc. *Dose:* 0.2 to 1.0 Gm. (3 to 15 grains) (0.25 Gm. = 4 grs., U. S. P.).

Pepsin will (practically) digest only in an acid medium (0.4% HCl is the best).

Preparations:

* *Pepsinum Saccharatum.—Saccharated Pepsin.*—Contains 1 part of the above pepsin, triturated with 9 parts of sugar of milk. It should digest 300 times its weight of egg-albumen. *Dose:* 0.3 to 4.0 Gm. (5 to 60 grains). Combined with Bismuth Subnitrate as powder, this is one of the favorite remedies in infantile diarrheas.

* *Liquor Pepsini* (N. F.).—Pepsin 4, Hydrochloric Acid 1.2, Glycerin 32, Water to 100. *Dose:* 4 to 8 c.c. (1 to 2 drachms).

* *Liquor Pepsini Aromaticus* (N. F.).—Contains 1.75% Pepsin, 1% of official Hydrochloric Acid (=⅓% absolute, Aromatics, Glycerin, and Water. (Each fluidrachm = 1 grain of Pepsin.)

* *Glyceritum Pepsini* (N. F., B. P.).—8.5% Pepsin, 1% Hydrochloric Acid, 50% each Glycerin and Water.

A similar preparation ("Essence of Pepsin") is made by extracting the stomachs directly with glycerin.

* *Elixir Pepsini* (N. F.).—1.75%.

* *Vinum Pepsini* (N. F.).—1.75%.

It is probable that the alcohol in the last two preparations causes a gradual deterioration in the activity of the ferment.

Pancreatinum (U. S. P.).—*Pancreatin.* A mixture of ferments prepared from pigs' pancreas. Occurs as a dry powder, soluble in water. *Dose:* 0.5 Gm. = 7½ grs., U. S. P. Digests best in alkaline solution (1% Sodium Carbonate), but also somewhat in a very weakly acid solution (0.1% HCl).

At least four ferments are present: Trypsin (acting on proteids); amylopsin (starch); steapsin (fats); and lactase (inverting lactose). The proteolytic digestion goes farther than that produced by pepsin; care must therefore be taken in artificial digestions that the process is not carried too far. Pancreatin should digest 25 times its weight of starch.

Liquor Pancreatis (B. P.).—2 c.c. should digest 80 c.c. of milk.

* *Enterokinase.*—A ferment contained in extracts of the duodenum. Activates the proteolytic ferment of pancreatic juice. Not used therapeutically.

* *Papain* (*Papoid, Plant Pepsin*).—A proteolytic ferment from the juice of the unripe fruit of *Carica Papaya. Dose:* 0.1 to 0.5 Gm. (2 to 8 grains). For solution of false membranes, used in 5% solution. Digests in either acid or alkaline medium (not in neutral). The commercial preparations are often inactive.

A number of other plants (Drosera, etc.) contain similar ferments.

* *Ingluvin.*—The dried and powdered membrane of chicken's craw. Claimed to be especially useful in the vomiting of pregnancy. *Dose:* 0.5 Gm., one-half hour after meals, followed by 30 c.c. (1 ounce) of 1% (official) Hydrochloric Acid. Claims probably exaggerated.

II. Amylolytic Ferments.

Pancreatinum (see above) also possesses an amylolytic ferment.

Maltum (U. S. P.).—Malt. The grain of barley (*Hordeum distichon*), partially germinated artificially, and then dried.

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* Not official.

Study Materia Medica Lesson 55.

Extractum Malti (U. S. P.).—A watery extract of malt, prepared at 55° C., and evaporated at this temperature to the consistence of a thick honey. Contains *diastase,* which digests starch in neutral or slightly alkaline medium. The extract is rich in carbohydrates, and has therefore some food-value. *Dose:* 16 c. c. = 4 ʒ, U. S. P. Many *liquid malt extracts* are in reality strong beers.

An analogous ferment is isolated from a Japanese mould, Aspergillus oryzæ, and marketed under the name of *Taka-diastase. Dose:* 0.1 to 0.3 Gm. (2 to 5 grains).

(B) SUMMMARY OF THE THERAPEUTICS OF DIGESTION.

Notwithstanding the splendid work which has been done of recent years in the investigation of the dyspepsias, the causes of these conditions are still very imperfectly understood, and the treatment is essentially symptomatic. However, if carefully carried out, the removal of the symptoms is generally followed by more permanent improvement. The most important measure in this respect is perhaps a proper *regulation of the diet.* The subject of dietetics cannot be entered into in this treatise, nor can any rules of general applicability be laid down. An intelligent patient can give the best indications as to the diet which is best adapted to his particular case, and if this is adhered to for sufficient time improvement usually results.

Any attempt at a rational therapeutic treatment can only be based upon a thorough physical and chemic examination of the existing conditions; else it cannot be anything but empirical and haphazard, apt to do more mischief than good. When the pathologic state is well understood, we may, from our knowledge of the physiology of digestion and the methods by which this may be modified, arrive at the theoretic indications and the manner in which these should be met. Clinical observations made with all the aids of modern science are as yet hardly sufficiently numerous to bear out these theoretic data.

The **indications** are as follows:

(A) Gastritis, Acute or Chronic.—*1. Removal of the irritant,* whether toxic, undigested food, or toxic products arising from these. These indications are met by emptying the stomach. In acute cases this may be done by *emetics,* or in either acute or chronic cases by *lavage.*

2. If the cause lies in *fermentation,* the lavage should be carried out in weakly antiseptic and acid solutions. The

antiseptics must, of course, be devoid of marked toxicity. Boric acid, salicylic acid, salol or resorcin are well adapted. The *acidity* should be that of the normal gastric juice, or about 0.2% HCl.

3. Protection of the organs against irritation. This may be done by *demulcents.* Especially in chronic cases, it is best to employ those which are at once nutritive, such as milk or eggs. With irritant poisons mucilage or oil may be more effectual.

4. Physiologic Rest.— This may be secured by using food with the minimum of indigestible residue and the maximum of nutritive value to a given bulk. It should be as free as possible from large particles, and it may be necessary to use it entirely in liquid form. In some cases it will be necessary to have the food largely predigested.

5. In the chronic form a *mild irritation* may be indicated. This may be secured by carbonated waters, by salts, or by the general group of stomachics — bitters, light alcoholic beverages, carminatives, etc.

(B) Hyper secretion of mucus demands *lavage.* This is rendered more efficient if a small quantity of *alkali,* most usually sodium bicarbonate, is added. The latter is frequently beneficial even without lavage. The *astringents* may also be useful, especially bismuth in the form of subnitrate.

(C) Anacidity demands the administration of *acids* and *bitter stomachics. Alkalies* are contraindicated.

Hyperacidity causes irritation, and should be removed by *alkalies.* The irritation may be lessened by the administration of demulcents or of oils.

(D) Absence of Ferments.— The ferments were supposed to be lessened in many chronic diseases, as chlorosis, tuberculosis, etc. There is no proof for this belief, and they are generally much less subject to change than the acid-secretion. It is established that they are often deficient in chronic gastritis, in carcinoma, and in certain nervous dyspepsias; whilst they are increased in other cases of the latter and in ulcers. However, it is doubtful whether the ferment action of the stomach is very important.

Deficiency of *pepsin* may be met by the introduction of the artificially prepared ferment. Notwithstanding the doubts which may be entertained as to its theoretic indication, it appears to give clinical results, and can do no harm.

Papain has the advantage of digesting in all media. The advantages of ingluvin are perhaps doubtful. Pancreatin can do no good, since it is destroyed in the stomach.

The secretion of ferments may be stimulated in a more rational manner by *stomachics.*

(E) The symptoms of dyspepsia are as often due to **motor deficiencies** as to faulty chemic digestion. The indications in this condition are met by lavage; small amounts of food taken at frequent but regular intervals; the prevention of fermentation by acids; the application of cold and electricity; the administration of salts or nux vomica.

(F) Many cases of dyspepsia are purely **nervous;** *i. e.,* unconnected with any pathologic alteration. In these cases the education of the patient to greater confidence is of most importance. Of drugs, caffein, nux vomica, and bromids are variously successful.

Some of the clinical symptoms may become sufficiently prominent to require special treatment. *Pain* can be relieved by heat, or if necessary by narcotics; *gas* by sodium bicarbonate; *anorexia* by stomachics; *bad taste* by aromatics (myrrh).

Intestinal digestion seems to require no special aid unless bacterial processes supervene, when a purge will answer the indication. If, however, the intestine is the seat of inflammation, or when excessive food is needed, it may be well to lessen its labor by the administration of predigested foods.

(C) NUTRIENTS.

Another class of diseases in which the digestion needs special attention comprises those in which forced nutrition is indicated. These require care not to overtax the digestive organs, an object which may be secured by the proper selection of the food and by artificial predigestion. The subject of dietetics cannot be entered into here in its hygienic aspects, but only in so far as it relates to therapeutics. The subject of infant feeding is left for special text-books. The treatment of obesity and diabetes is also studied preferably in connection with these diseases.

In discussing the different kinds of nutrients, we will follow the usual classification into proteids, fats, and carbohydrates; but it must be remembered that all three classes must be administered to secure the required object.

1. Proteids.—Of the various **meats,** young lean beef is in most cases the most easily digested. The white meat of fowl enjoys a special reputation, and whilst most clinicians support this, no chemic differences between it and the dark meat have yet been demonstrated. *Cooking* in any form, while it lessens the digestibility *in vitro*, develops aromatic products which act as stomachics. *Raw meat,* finely scraped, is very highly nutritious and easily digested. It is usually flavored with a little scraped onion, salt, etc. Care must be taken that it does not contain parasites. It has been claimed that dogs fed on raw meat resist tuberculous infection better than ordinary animals.

Eggs present proteids in a very digestible form, especially when soft boiled. They have the disadvantage that they soon become tiresome. **Milk** contains not only proteids, but also carbohydrates and fats. It also quickly becomes tiresome to adults, and, further, it has a tendency to produce constipation. The former objection may be obviated by giving it in different forms, such as curd produced by rennet, as koumiss, etc. The proteid of milk — **cheese** — is very rich in assimilable nitrogen, but it is often not very digestible. The casein is precipitated from the milk in the stomach by the rennin and acid. This curd is finer, and therefore more digestible, if barley water[1] is added to the milk.

The **proteids of vegetables** are less easily assimilable than those of animal origin. They require very thorough cooking. Legumes are liable to give rise to flatulence and diarrhea, through bacterial decomposition of their carbohydrate constituents.

Gelatin, although not a true proteid, contains a large percentage of nitrogen, and it may replace the proteid constituents of the food to some extent (as usually given, by about 25%), but not entirely. It is easily digested.

Types of Proteid Preparations.— The various commercial and domestic products may be reduced to the following types:

(a) Bouillon and Meat Extracts.— Bouillon (beef-tea) is prepared by boiling meat with water; the extracts by evaporating the solution to a semi-solid consistency. The coagulable proteids are removed by this process, the extract containing the salts of the meat, the flavoring substances and meat bases (xanthin and creatin products) and a certain amount of non-coagulable proteid, in the form of gelatin, albumoses, etc. In the small amounts in which they are used, these preparations contain a *very insignificant quantity of nutriment.* They are, however, *valuable as stimulants.* They owe their action largely to the odorous principles which they contain, and which are excellent stomachics.

The potassium salts have also been invoked to explain the action, it being claimed that they stimulate the heart in moderate doses and paralyze it in large doses. But the dose required to produce the former effect is very much larger than would be administered in beef-tea.

The **meat bases** (xanthin, hypoxanthin, creatin; etc.) probably participate in the stimulating actions. They are closely related to the caffein group (Chapter VIII), since they are all purin derivatives. These are especially abundant in cellular tissues (thymus, spleen, etc.); the quantity in different varieties of meat is about the same. Peas, beans, oatmeal, asparagus, onions, and beer also contain notable proportions. They have been blamed for the production of gout, but on insufficient evidence. Nevertheless, a purin free diet (eggs, rice, and milk) seems to be beneficial in nephritis and eclampsia. About 50 to 60% of the ingested purins are excreted as such in the urine, furnishing the "exogenous" purin. The remainder is oxidized. A definite amount of the urinary purin is derived from cell metabolism (endogenous purin).

Bouillon.— One kilo of medium lean beef gives 2.5 L. bouillon of the following composition (Gautier):

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[1] *Barley water* is prepared by washing 1 part of barley, boiling for a short time with 4 parts of water, straining off the liquid, and boiling the remaining barley with 30 parts of water down to 15 parts and straining.

(BOUILLON) PER LITER.

Albuminoids	7.5	Gelatin	1.72
		Albumose	0.48
		Peptone	5.30
Creatin Bases	0.9		
Xanthin	0.25		
Taurin, etc.	0.12		
Inosit and Glycogen	1.40		
Lactic acid	0.20		
Extractives	4.60		
Soluble mineral salts	3.76	$FeHPO_4$	0.02
Insoluble mineral salts	0.38	HCl	0.72
		$CaHPO_4$	0.12
		NaCl	0.15
		K_2SO_4	0.35
		K_2HPO_4	2.60
		$MgHPO_4$	0.23
	19.11		

Beef-tea made with dilute HCl (0.2% to 0.4%) instead of water. It would seem on theoretic grounds that this could be made quite nutritious, although there are few clinical data. Alkali albuminates derange the stomach.

* *Extractum Carnis Liebig.*— Beef-extract.— An evaporated decoction of meat.

Composition of Liebig's Extract:

PER CENT. (GAUTIER.)

Water	15.26		
Coagulable proteids	0.05	Albuminoids	36.93
Gelatin	8.49		
Albumose	2.32		
Peptone	26.07		
Creatin bases	8.30		
Xanthin bases	0.89		
Inosit and glycogen	2.20 to 4.25		
Extractive matter	11.98		
Soluble mineral salts	21.26		
Insoluble mineral salts	1.13		

Any other similar preparation of meat-extract may be used instead.[1]

* *Vinum Carnis* (N. F.).— *Wine of Beef:* 3.5% Liebig's extract in sherry wine.

* *Vinum Carnis et Ferri* (N. F.).— *Beef, Iron, and Wine:* The preceding with ⅓% of iron chlorid.

* *Vinum Carnis, Ferri et Cinchonæ* (N. F.) contains, in addition, 0.3% cinchona alkaloids.

(b) Beef Juices.— Tissue fluid, expressed from meat without heat. Their advantage lies simply in the mechanical removal of the fibers. They contain 6% to 12% of coagulable proteid, and theoretically at least, it is difficult to see in what way they would be superior to raw eggs mixed with beef-tea, which would be very much cheaper. Perhaps they are more digestible.

(c) Insoluble Meat Powders.— These are only important as cheap meat substitutes. They consist of the poorer parts of meat, or of vegetable proteids, rendered inodorous by prolonged boiling with oxidizing agents. *Tropon* (⅓ animal and ⅔ vegetable proteid); *Soson* (milk); *Roborat* (cereals) may be counted in this class.

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[1] The chemical composition of a number of meat extracts, etc., is given by McGill, 1899.

* Not official.

(d) Casein Products.— A large number of casein products have been placed on the market. They present a very concentrated form of assimilable proteid food, which may be added to soup or baked into bread. (Daily dose = 15 to 45 Gm. — 2 to 6 even tablespoons.) Their concentration makes them valuable in anorexia, whilst the absence of purin derivatives makes them preferable to meats in nephritis and uric acid diathesis. They can be prepared much more cheaply than meat products.

Fresh Casein can be prepared at home by coagulating skim-milk at 28 or 30° C. with rennet, and straining after ¾ hour.

The commercial products (which are much more expensive) are for the most part casein-salts of alkalies: They constitute tasteless powders, soluble in water, containing about 13% of nitrogen. The most important are: *Plasmon* and *Nutrose* (*sodium* compounds); *Eukasin* (ammonium), and *Sanatogen* (calcium glycerinophosphate); Galactogen, Eulactol.

These products have alkaline properties, which may be objectionable. This is avoided in *Sanose,* in which the casein is emulsified by the addition of 25% of albumose.[1]

(e) Predigestion of Foods of all Kinds.— This is undertaken with the view of relieving the digestive organs of part of their labor. It is especially useful in rectal alimentation.

Carbohydrates may be converted into glucose; fats may be emulsified; and *proteids* may be converted into acid or alkali-albumin and into albumoses, etc. It has been found experimentally that these derived proteids can completely replace the native proteids of the diet, and it may be assumed that they tax the digestive organs less. If the predigestion is carried beyond the stage of albumoses, the result is less satisfactory; the final products of pancreatic digestion especially are useless to the body. Furthermore, excessive digestion imparts a disagreeable bitter taste and renders the preparations irritant, so that it must be avoided. The taste is less marked if strict asepsis is observed during the digestion. It can also be disguised by the addition of aromatics or of meat extract.

The means employed for predigestion are various. Starches are boiled and then treated with diastase of any kind, most commonly in the form of malt extracts. Fats are emulsified mechanically. For mixed foods, such as milk, pancreatin is preferred. For proteids, peptic digestion or prolonged heating with dilute acids is preferred.

Many of these predigestions can be done economically at home.

General Rules for the Preparation of Predigested Foods of All Kinds.— The meat should be lean and finely hashed. Starch should be boiled. The mixture is brought to about blood heat, the ferment added, and the heating continued at this temperature for one-half hour (milk), or two or three hours (meat).

The quantity of ferment to be employed and the *reaction of the medium* are as follows, using the United States Pharmacopœial preparations:

Pancreatin, Milk: For 1 pint take 5 grains pancreatin and 20 grains sodium bicarbonate.[2]

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[1] The literature of artificial proteid foods is given by Hultgren, 1902.

[2] *Pancreatin and Soda Tablets,* containing 0.15 Gm. of pancreatin and 0.5 Gm. of sodium bicarbonate, are manufactured. A tablet suffices for the digestion of half a pint of milk.

Rennet, Milk: For 1 pint take ½ drachm Liquor Seriparus, N. F.
Pepsin, Meat: For 1 pound take 3 pints water, 2 drachms pepsin, 1 ounce dilute HCl, U. S. P. Flavor with meat extract.

(f) Commercial Predigested Foods, Solid.— The meat products consist mainly of albumoses, although they are commonly called "peptones."

* *Witte's peptone* is not used as a food, on account of its bitter taste.

* *Somatose* appears to be the most practical form of administering meat albumoses. It occurs as a soluble, almost tasteless, powder, which is stirred into coffee, gruel, etc. Its *dose* for adults is given as 10 to 15 Gm. per day. A similar product, Milk-Somatose, is obtainable from milk.

By evaporating carefully prepared peptic meat-digests to a syrupy consistency, an extract can be obtained which contains sufficient nitrogen to be available as food; when it is flavored with meat extract and condiments, it is not unpalatable.

(g) Liquid Predigested Foods (*Liquid Peptonoids, Panopeptone, etc.*).— These proprietary preparations contain 5 to 6% of peptonized proteid, 12.5 to 16% of carbohydrates (saccharose, dextrin, and glucose); and 14 to 17% of alcohol. The proteid-content is about 1½ times that of milk, the carbohydrates about three times. The daily dose (3 to 12 tablespoons) would represent only 0.4 to 1.6 Gms. of nitrogen, and 7 to 28 Gms. of carbohydrates. It is evident that their food-value is of little significance. The "restorative" qualities claimed for these products are due to the alcohol which they contain, and are in no sense "marvellous."

2. Fats.— Fats are the most extensive source of energy, and they may to a certain degree save proteids. They are especially useful in conditions of emaciation, such as are found in tuberculosis, etc.

The digestion of fats in large amounts presents considerable difficulty. Since they are practically insoluble, it is evident that their absorption will be largely facilitated by having them in very fine subdivision; in other words, by emulsification. The fats which are fluid at body temperature are therefore more easily digested than those which are solid (Moore, 1904). There is no material difference in the digestibility of animal and vegetable fats.

The emulsification is very greatly favored by the presence of free fatty acids, which can form soaps with the sodium carbonate of the intestinal fluid; these soaps act as emulsifiers. The digestibility of the different fats is therefore generally proportionate to the amount of free fatty acid contained in them.

Cod liver oil, which contains considerable free acid, is consequently the most easily digested (Buchheim, 1874). It also penetrates membranes readily, perhaps on account of its cholesterin content. Even large quantities are readily absorbed, although they may derange a delicate digestion; but they do not ordinarily cause caltharsis.

The superiority of this oil over other fats is so striking, that other explanations have been sought. The effect has been attributed to the non-fatty constituents, which may be removed by alcohol (constituting the so-called extracts, or "*tasteless*" preparations); to the ptomains, cholesterin, traces of iodin and bromin, etc. The evidence for this theory is very weak. These products are certainly worthless nutrients. On the other hand, an artificial substitute for cod liver oil, made by adding 1 part of oleic acid to 6 of olive oil (lipanin), has been fairly successful.

Oleum Morrhuæ (U. S. P., B. P.) (*Oleum Jecoris Aselli*).— *Cod*

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* Not official.
Study Materia Medica Lesson 55.

Liver Oil.— A fixed oil from the fresh livers of *Gadus Morrhua* and other species, Pisces.

Besides the ordinary constituents of animal fats, it contains a large proportion of free fatty acids; it also contains biliary constituents and traces of iodin and phosphorus and ptomains, the quantity of the latter varying with the time that the livers have lain before the extraction of the oil.

Dose: 8 to 15 c. c. (2 to 4 drachms), best given in emulsion.

Emulsum Olei Morrhuæ (U. S. P.— 50% of the oil, emulsified with acacia, and flavored with oil of gaultheria. Any other flavor may be specified. *Dose:* twice the preceding (8 c. c. = 2 ʒ, U. S. P.).

Emuls. Ol. Morrh. cum Hypophosphitibus (U. S. P.).— The above emulsion, with the addition of the hypophosphites of calcium, potassium, and sodium. *Dose:* as the preceding.

Emulsions of petroleum have also been introduced as nutrients, but are entirely unabsorbable and without action, except as intestinal emollients (Hutchison, 1899).

Butter is also very digestible, since the globules of fat which form it are in a state of fine subdivision. This, of course, does not hold true of butter which has been melted, and which is no more digestible than other melted fats.

The least digestible of fats is the fatty tissue in which the cells are intact, such as bacon, etc. However, a healthy individual is able to digest perfectly moderate amounts of any fat. The differences become important only when very large quantities must be taken, or when the digestion is deranged.

3. **Carbohydrates.**— These are also useful as sources of energy and possibly for the formation of fat. They cannot, however, save proteids as efficiently as the direct addition of fat to the diet. Carbohydrates may be given in the form of *starch* or *sugar.* Both are for the most part converted into glucose before being absorbed. The digestion presents considerable difficulty in the case of raw starch, so that a thorough boiling is essential. The finer starches (arrow-root, tapioca, sago, salep, etc.) used for invalids, possess mainly the advantage of a finer flavor.

The starches of the leguminous plants are not so easily digested as those of the cereals. Starches may also be predigested by malting. Such preparations found on the market as "*malted foods*" are superior to glucose or cane-sugar by causing less gastric irritation.

Decoctions made from *Irish and Iceland moss* also serve to some extent as nutrients, but the gums of which they are constituted do not digest very readily. *Glycerin* also aids in saving the proteids to a small extent, but would not be given as food. The rules for *alcohol* have been discussed in connection with this drug (see Index).

Levulose has been recommended as a substitute for sugar in diabetes. since it is utilizable when other carbohydrates are not. It occurs on the market as *Diabetin.* Its use has not, however, become very popular.

MATERIA MEDICA.

Saccharum.— See Index.

Amylum.—*Starch.*— The official is the corn-starch, but the other starches act similarly. They are also used as nutrients. Arrow-root is often given for the latter purpose. They are boiled with water; the flour may also be used, but is not as smooth:

Amylum (Maidis) = corn-starch.
" Tritici = wheat starch.
" Oryzæ = rice starch.

Tapioca, Sago, etc., belong rather to the nutrients.

The starches may be distinguished microscopically (Fig. 1, page 22).

Oatmeal porridge is a convenient way of administering pills or powders, these being placed in the center of some of the porridge in a spoon.

Other demulcents, not quite as often used for this purpose, are the following. They are all used as decoctions:

* *Salep.*— The tuber of various species of Orchis; contains gum and starch.

* **Dextrinum.**— *Dextrin.*— Prepared by heating starch with nitric acid. Presents all the characters of gum arabic, and forms the principal ingredient of *commercial mucilages.* A good formula for this is the following (Sykes): Mix 180 Gm. of dextrin with 180 c.c. cold water; add 240 c.c. boiling water and boil five minutes, stirring constantly. Add hot water q. s. 400 c.c. When cold, add 30 c.c. dilute acetic acid, 10 drops carbolic acid, and 30 c.c. of glycerin, previously mixed.

Rectal Feeding.— This becomes necessary when alimentation by the mouth is inadmissible. Carbohydrates are well absorbed by this channel; fats, undigested proteids, milk and casein poorly. The absorbability may be increased by pancreatic predigestion (Reach). Rectal alimentation suffices for only a limited time, varying with the previous condition of the patient, especially as regards adipose tissue.[1]

The food is introduced into the rectum in the form of enemata. These must be made as non-irritant as possible; *i. e.,* they must not be too concentrated, and must be used in small quantities, of 1 to 8 ounces at each injection. The constituents must of course all be in the liquid form.

Subcutaneous feeding— alimentation by subcutaneous injections— has also been attempted. This is impracticable for proteids and carbohydrates, for their injection causes a nephritis if they are used for some time. Nor are they of any use as nutrients, for while the proteids are burned in the organism, they do not seem to save any other constituents, and animals die even more quickly than when simply starved. Glucose is utilized somewhat more efficiently, dextrin and glyogen only moderately, and saccharose scarcely at all (Mendel and Mitchell, 1905). *Oil,* however, can be very well given by this method; 10 to 100 Gm. per day of olive oil being slowly injected into the subcutaneous tissues with the same technique as is used for the injection of antitoxic serums. The absorption, however, is so slow that these injections are almost worthless (Winternitz, 1903; Henderson and Crofutt, 1905).

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[1] A patient may be kept alive for 6 days by the exclusive use of three enemata per day, each containing 250 c.c. of milk, one yolk of egg, one knife point of salt, with some flour and claret.

(D) GENERAL TONICS AND ALTERATIVES.

These terms are used very loosely. They relate to purely clinical phenomena, without taking into account the underlying action. As therapeutic groups, therefore, they include a very heterogeneous collection of remedies.

Tonics are defined as remedies which improve the general health, vigor, and energy of the patient; *Alteratives,* as those which alter metabolism. The latter are usually employed for the production of tonic effects.

Tonics and Alteratives are found generally useful in all conditions in which there is faulty nutrition. This may arise from faults of diet or digestion; from excessive or insufficient use of tissue; from faulty oxidation or excretion of waste-products; or from other perversions of metabolism not at present understood. Such conditions occur almost invariably in the course of chronic disease or poisoning. In other words, whenever one or more organs are prevented from fulfilling their function in a normal manner, the nutrition of the whole body suffers, and the phenomena of general lassitude, want of energy, nervousness, neurasthenia, etc., make their appearance.

When the underlying cause can be discovered and removed, this will also remove the symptoms. But in many cases this is impossible, and the conditions must be treated symptomatically. Certain tonic measures are then always indicated and of benefit: Diet, attention to the stomach and intestine, stomachics and nutrients, hygiene, exercise, or rest, baths, climate. Certain "nerve-tonics" are also generally useful. These are drugs which increase the irritability of the spinal cord, and hence the reflex tone, which is usually low in these conditions. Strychnin is the most typical of this class.

When the cachexia is more profound,— as in tuberculosis, tumors, anemias, in the "dyscratic diseases,"— these tonics will scarcely be sufficient, although always useful. Recourse is then had to *alteratives.*

The value of this class of drugs was established empirically, and was at first considered more than doubtful, when the critical spirit of rational therapeutics subjected them to scientific inquiry. Direct experiments intended to demonstrate their action upon metabolism gave very inconstant results, nor were the clinical data at all uniform. However, experience speaks so strongly in their favor that most modern pharmacologists and clinicians acknowledge their action.

The inconstant results are not surprising. Indeed, we know much less about their action than is generally supposed. When we stop to consider that even in metabolism-experiments on animals at least three factors are involved — absorption, metabolism, and excretion — and that each of these will be modified by a number of side-actions, it will be plain that the results will not be easy to interpret. A consultation of the original literature impresses one with the fact that the increase or decrease of nitrogen excretion noted in most experiments, and quoted as decisive in most text-books on therapeutics, is so small as to fall within the natural variations, and may be purely accidental. Indeed, the number of drugs of whose effect on metabolism we can feel certain is growing less and less. Nor are we any better off in regard to the disturbance of metabolism in the diseases themselves. In such diseases as scurvy, gout, diabetes, phthisis, chlorosis, and carcinoma, where there is undoubtedly marked nutritive derangement, the study of the metabolism by our present methods presents no striking peculiarities. The fact of the matter is, that the examination of the end-products gives us but very little indication of what really occurs in metabolism, and yields but very little insight into what appear to be some of its most important phases. We may conceive, for instance, that the amount of N absorbed and excreted is quite normal, but that in its disassimilation, the molecule fails to pass through some particular stage necessary to the organism.

The pharmacologist may predict that for certain reasons a certain poison is bound to produce *some* modification in tissue change. The clinician may record that it is beneficial in a certain proportion of cachectic disease of a certain type. But as long as the former cannot predict the nature of the change in all its phases, nor the latter explain the nature of the condition which he finds benefited, so long will a rational application of alteratives be impossible. They must be tried empirically in every case, one after the other. Used in this way, they are often very serviceable.

The principal exceptions to this empiricism are the benefits of thyroid in thyroid disease and in obesity; of ovarian substance in post-climacteric conditions; and possibly those of mercury in syphilis.

From a pharmacologic standpoint we may conceive the action of these substances on the cells as being due to:

1. Irritation as molecular foreign bodies (neutral salts, especially iodids; alcohol).
2. Change of reaction of tissues (acids or alkalies).
3. Direct diminution of oxidative changes (P, As) or N metabolism (quinin).
4. Substitution of their own molecules for those of the tissues (alcohol, fats).

The numerous vegetable alteratives are either entirely inactive or owe their action to the presence of bitter or cathartic principles, and are discussed in those groups.

MATERIA MEDICA.

Guaiaci Lignum (B. P.).— The heart-wood of *Guaiacum officinale*, Zygophylleæ; West Indies and other parts of America. Contains 20 to 25% of the Resin and some saponin (a trace of the latter is also contained in the resin). There is some reason to believe that the saponin is the bearer of the action, which is nauseant and purgative. Guaiac is an almost obsolete remedy for syphilis, gout, rheumatism, tuberculosis, etc. It was introduced soon after the discovery of America.

Guaiacum (U. S. P.) [*Guaiaci Resina*, B. P.] (Gum Guaiac).— The resin of the above. 85% of this is sol. in alcohol. It contains a number of resinous acids, especially guaiaconic acid, which is colored blue by oxidation. *Dose:* 1 Gm. = 15 grs.

Mistura Guaiaci (B. P.).— *Dose:* 15 to 30 c. c. (½ to 1 oz.).

Tinctura Guaiaci (U. S. P.).— 20%. Alcohol. 4 c. c. = 1 ʒ.

Tinctura Guaiaci Ammoniata (U. S. P., B. P.).— 20%. Made with aromatic spirits of ammonia. 2 c. c. = 30 ♏.

Trochisci Guaiaci Resinæ (B. P.).— Each contains 0.2 Gm. (3 grs.). *Dose:* 2 to 4 c. c.

Sabal (U. S. P.).— (*Saw Palmetto.*)— The partially dried ripe fruit of *Serenoa serrulata*, Palmæ. Statements as to presence of alkaloids and volatile oils are contradictory. Recommended as nutritive tonic, alterative, in respiratory diseases, digestive disturbances, as aphrodisiac, etc., etc. Of very doubtful value. *Dose:* 1 Gm. = 15 grs., U. S. P.

* *Jambul.*— The fruit, leaf, or bark of *Syzygium Jambulana*, Myrtaceæ, Eastern Asia. It contains an essential oil, tannin, and probably a glucosid. It has been recommended in Diabetes Mellitus in *doses* of 0.3 to 0.5 Gm. of the fruit (5 to 8 grains). Efficiency doubtful.

* *Chaulmoogra Oil.*— A fixed oil from the seeds of *Gynocardia odorata*, Bixineæ, Malay peninsula and North-eastern India. Of temporary benefit in leprosy, but does not give permanent cure. Its stoppage causes collapse. The use is purely empirical. As it becomes very nauseating, it is best given hypodermically, in *doses* of 0.3 to 0.8 Gm. (5 to 10 drops). The oral dose is 1 to 3 Gm. (15 to 45 grains) per day.

The oil is buttery, of greenish yellow color and peculiar odor and taste. It contains 18% of gyno-cardic acid, which has also been used, in *doses* of 0.03 to 0.2 Gm. (½ to 3 grains).

(Power and Barrowcliff state that the ordinary oil is derived from the seeds of *Taraktogenos Kurzii*).

* *Echinacea.*— The root of *Echinacea augustifolia*, Compositæ, Western United States. Advanced as sialogogue, diaphoretic, and general alterative. The claims appear extravagant. *Dose,* 1 to 2 Gms., (15 to 30 grains). (Lloyd, 1904; Madden, 1905.)

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* **Not official.**

PART III.

LABORATORY COURSE IN PHARMACOLOGY.

CHAPTER XXXIII.

INTRODUCTION.

The Objects and Methods of Laboratory Instruction.— It seems quite superfluous, at this time, to insist on the great value of laboratory instruction. It may be well, however, to summarize the objects which it must keep in view. These consist in imparting information, in developing an understanding of the subject, and in acquiring a technical training. The information which can be derived directly from laboratory work forms the proper basis of didactic instruction: It facilitates the understanding of those facts which are deduced from experiments; it illustrates their value and their limitations; it impresses them on the memory. The training of a laboratory course cultivates manual dexterity, and what is more important, it fosters the "scientific spirit"— the judicial attitude of mind which requires the objective demonstration of all statements and theories, and which deduces from these objective data the conclusions which they justify— no more and no less. The ultimate goal of this instruction should be, to enable the student to deal critically and independently with the matter which is presented to him; to give him a more vital grasp of the whole subject of pharmacologic knowledge; and to generate and stimulate a healthy thirst for further information.

The course of instruction which will meet these requirements in the best attainable manner must vary somewhat with the resources at the command of the department; with the size of the classes; and with the special qualifications of the students and instructors. This applies particularly to the total time which can be devoted to laboratory work, and its apportionment to class-demonstrations and to individual work by the students. The most thorough training would probably be obtained if the student were to perform every experiment for himself, with a minimum of aid from the instructor. The time which would be required for this purpose is, however, quite prohibitive; nor is this plan essential. Demonstrations — arranged in such a manner that every student can see the experiment, and so that as many as possible may assist in its performance — are almost as useful as regards the information acquired, and can be substituted for a considerable number of individual experiments in regard to the training; especially if the student has himself performed similar experiments. They cannot, however, replace individual work completely, and as much of this should be given as time and material permit. The demonstrations are advantageously shown in connection with the individual laboratory work; the students being called from their experiments to watch the results of the demonstrations. This economizes time when lengthy preparation or intermittent observations are involved; it facilitates the co-operation of the students and demonstrators; and it emphasizes the close relation of the demonstrations and of the individual work. Another expedient of economy, which is extensively utilized in this course, consists in having parts of the class perform analogous experiments, but with different drugs; the results of each section being demonstrated and reported to the entire class. A great deal of time can also be saved by having the apparatus and reagents in good order, systematically arranged, and conveniently accessible. The student should co-operate in this by keeping his working-place neat and clean.

Even with the closest management of the time, it is naturally impossible to present every possible pharmacologic experiment to the class. Those experiments should be selected which demonstrate fundamental facts and methods in the simplest manner. Experiments which consume much time, or which are beset with special difficulties, or which are so exposed to accidents that they are more apt to fail than to succeed in the hands of elementary students, are not suited to the conditions of an ordinary laboratory course, and may be left to advanced students who wish to devote extra time to the subjects. Brief directions for some of these experiments, and also for those which are ordinarily performed in the physiology course, are introduced as "optional experiments." These should be studied by all students. They can be extended indefinitely by the use of the dose-tables in Chapter XXXIX. The regular experiments, which are described in Chapters XXXV to XXXVII, are sufficient for the general medical curriculum, in the author's opinion.

The mere performance of these experiments has only a very limited value if the student does not study them exhaustively. He should have a definite conception of the object of each experiment before he undertakes its performance; and he should render to himself an account of every step of the process, and of the conclusions to which it leads. The student's note-book is therefore a very essential part of the course. Nothing cultivates the powers of observation like the taking of careful, detailed notes during the progress of the experiment; whilst the critical faculty is stimulated by the condensation of these detailed results into brief and definite conclusions. This applies particularly to the animal experiments. The constancy or variability of the results are illustrated by comparing the results of different members of the class, and of preceding classes. For this purpose, it is well to appoint a class-reporter for each exercise, with the duty of collecting and comparing all the results; these reports being kept on file for the use of succeeding classes. They should be read and discussed in the laboratory conferences.

Teachers differ in opinion as to whether the objects of the experiments and the expected results should be pointed out to the student in advance. In a pharmacology course, the author believes that it is more useful to do so, on account of the complexity of the subject, and the large ground which has to be covered.

Relation of the Laboratory and Didactic Instruction.— The laboratory course may be treated either as an adjunct to, or as the basis of, the didactic instruction. If it is intended to illustrate the didactic teaching, it should keep step with the latter; the experiments should be arranged with reference to each drug. The summary-index in Chapter XXXVIII indicates this arrangement. In the author's opinion, however, the course is much more valuable if it is made the basis of the pharmacologic instruction; if it is used to deduce the facts. rather than to illustrate them. For this purpose, the laboratory course should precede the didactic instruction; and the exercises should be arranged with a view to the pharmacology of particular organs, and the methods used in their investigation, rather than with regard to the individual drugs. If the conclusions are correctly drawn, and summarized as in Chapter XXXVIII, the student will enter on the didactic study with a fairly extensive, first-hand knowledge of the principal facts; the purpose of the didactic instruction being, to correlate, apply, and extend these facts.

An elementary laboratory course is of necessity somewhat unevenly balanced. It is much better suited for the development of some facts than of others; and undue stress seems therefore to be placed on the former. The "explanatory" notes and the "introductory" exercises are inserted to meet this objection. These are made as elementary as possible, to keep them within the scope of the experimental knowledge of the student. Even with these, however, it is impossible at times to avoid an exaggeration of the laboratory side of the subject, and a comparative neglect of features which may be of greater practical therapeutic importance. This drawback should not be vital, for the didactic study should restore the balance. Attention should also be called to this subject by the demonstrators, whenever necessary. The text-book references at the beginning of each exercise will be useful for this purpose; they need not be consulted by the strudent, but are for the guidance of the instructors. The student, however, should always consult the references to other exercises.

The multiplicity of phenomena and problems which arise in the course of the animal experiments, renders thorough supervision of the work indispensable. The size of each class should therefore not exceed 30 to 40 men, and a demonstrator should be appointed for every 12 students, if possible. These may be selected from the members of the more advanced classes.

Arrangement of the Course, and Time Required for the Experiments.—These are subjects which are governed so largely by local circumstances, that no general rules can be given. The following schema may, however, serve as a guide: The elementary subjects and the laboratory work are placed in the second year; the didactic study of the drugs mainly in the third year. This brings the animal work into the last weeks of the second year when the student is well advanced in physiology; whilst the didactic work coincides with the clinical teaching.

The schema requires, for the sophomore year, 3 hours per week during the first 20 weeks, and 8 hours per week for the last 10 weeks (a total of about 30 hours of lectures and recitations, and 110 hours of laboratory work and conferences). The lectures and recitations in the Junior year take up about 60 hours.

TABLE XVI.—ARRANGEMENT OF TIME AND SUBJECTS IN THE SOPHOMORE YEAR.

(The laboratory work and demonstrations are in italics.)

First Week:	Hours.
(*a*) Introductory Lecture (Read Chapter XXXIII).	One.
(*b*) *Demonstration of Gross Pharmacognosy* (Ex. 1).	
(*c*) Lecture on Histologic Pharmacognosy.	
(*d*) *Assignment of Lockers.*	Two.
(*e*) *Study of Plant Histology* (Ex. 2).	
(*f*) *Alkaloidal Reactions* (Ex. 3, I).	

	Hours.
Second Week:	
(*a*) Recitation on Definitions and (*b*) Plant Anatomy, gross and microscopic (Chapter I, p. 17 to 19, 26 to 32; and Ex. 1 and 2).	One.
(*c*) *Complete Plant Constituents* (Ex. 3).	Two.
Third Week:	
(*a*) *Demonstration of Metrology* (Ex. 4). (*b*) Recitation on Plant Constituents (Chapter I p. 19 to 20; and Ex. 3).	One.
(*c*) Lecture, and *Demonstration of Pharmaceutic Methods* (Ex. 5). (*d*) *Demonstration of Dispensing* (Ex. 7).	Two.
Fourth Week:	
(*a*) Recitation on Metrology and General Pharmaceutic Methods (p. 32 to 56).	One.
(*b*) *Dispensing* (Ex. 7).	Two.
Fifth Week:	
(*a*) Recitation on Aquæ to Decoctions (p. 56 to 61). (*b*) Review of Metrology.	One.
(*c*) *Incompatibilities* (Ex. 8, No. 1 to 12) (Read Ch. IV C.).	Two.
Sixth Week:	
(*a*) Recitation on Tinctures to Emulsions (p. 61 to 66). (*b*) Review questions.	One.
(*c*) *Demonstration of Assaying* (Ex. 9, No. II). (*d*) *Start Isolation of Alkaloids* (Ex. 9, No. I, 1 and 2). (*e*) *Incompatibilities* (Ex. 8, to No. 19).	Two.
Seventh Week:	
(*a*) Recitation on Solid Preparations to Assaying (inclusive) (p. 66 to 74).	One.
(*b*) *Complete Isolation of Alkaloids* (Ex. 9) *and Incompatibilities* (Ex. 8).	Two.
Eighth Week:	
(*a*) Recitation on first two pages of Incompatibilities (p. 74 to 76; and Ex. 8). (*b*) Recitation on Toxicology, to Toxicologic Analysis (exclusive) (Ch. V, p. 79 to 81).	One.
(*c*) *Conference and Demonstration on Toxicologic Analysis* (Ch. V).	Two.

	HOURS.
Ninth Week:	
(*a*) Recitation on Incompatibilities (Ch. IV C, p. 76 and 77; and Ex. 8).	One.
(b) Recitation on Toxicologic Analysis (p. 81 to 87).	
(*c*) *Specific Reactions* (Ex. 10, No. I).	Two.
Tenth Week:	
(*a*) Recitation of Solubilities (Ch. IV C, p. 77 to 79)	One.
(*b*) Review of Incompatibilities and of Toxicologic Analysis (Ch. V).	
(*c*) *Specific Reactions* (Ex. 10, No. II and III).	Two.
Eleventh Week:	
(*a*) Review of Work to Date (p. 17 to 88).	One.
(*b*) *Specific Reactions* (Ex. 10, No. IV to end); Begin Suppl. of Ex. 10.	Two.
Twelfth Week:	
(*a*) Written Test on Work to Date (p. 17 to 88).	One.
(*b*) *Unknown Solutions* (Suppl. Ex. 10).	Two.
(*c*) *Begin Preservatives* (Ex. 11).	
Thirteenth Week:	
(*a*) Discussion of Test.	One.
(*b*) Recitation on Prescription Writing (p. 92 to 100).	
(*c*) *Finish Preservatives* (Ex. 11) *and all back work.*	Two.
(*d*) *Give out drugs for* Ex. 13.	
Fourteenth Week:	
(*a*) Review of tables (p. 97, 99, 100).	One.
(*b*) Recitations on General Principles of Flavoring (Ch. VI B, p. 100 to 102).	
(*c*) Practice in Prescription Writing.	
(*d*) *Drugs in Urine* (Ex. 13).	Two.
(*e*) *Chemic Antidotes* (Ex. 14, also Ch. V).	
(*f*) Study of Materia Medica.[1] Lesson 1.	
Fifteenth Week:	
(*a*) Recitation on Materia Medica, Lesson 1.	One.
(*b*) Prescription Writing.	
(*c*) *Corrosives and Irritants* (Ex. 15 to 18, incl.).	Two.
(*d*) Study of Materia Medica. Lesson 2.	
Sixteenth Week:	
(*a*) Recitation on Materia Medica, Lesson 2.	One.
(*b*) Recitation on Irritants and Corrosives (Ch. XXVIII A, p. 660 to 671; and Ex. 15 to 18).	

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[1] Appendix A. It may be necessary to enter the data outside of the regular class-hour.

	Hours.
(*c*) *Hemoglobin and Blood Corpuscles* (Ex. 21 and 22). (*d*) Study of Materia Medica. Lesson 3.	Two.
Seventeenth Week:	
(*a*) Recitation on Materia Medica. Lesson 3. (*b*) Recitation on Exercises 19 to 22. (*c*) Prescription Writing.	One.
(*d*) *Osmosis* (Ex. 23). (*e*) Prescription Writing. (*f*) Study of Materia Medica. Lesson 4.	Two.
Eighteenth Week:	
(*a*) Recitation on Materia Medica. Lesson 4. (*b*) Recitation on Osmosis (Ex. 23).	One.
(*c*) Prescription Writing. (*d*) Study of Materia Medica. Lesson 5.	Two.
Nineteenth Week:	
(*a*) Written Test and identification of Specimens, covering the work of the 13th to 18th week, inclusive; except prescription writing and Lesson 5 of Materia Medica.	One.
(*b*) Discussion of Test. (*c*) Recitation on Water to Sulphur, inclusive (p. 671 to 676; and Materia Medica, Lesson 5). (*d*) Prescription Writing. (*e*) Study of Materia Medica, Haloids, Lesson 6. (*f*) Read Chapter XXXIV, p. 792.	Two.
Twentieth Week:	
(*a*) Recitation on Acids and Haloids (p. 676 to 681; and Materia Medica, Lesson 6). (*b*) Prescription Writing.	One.
(*c*) *Assignment of Animal-Lockers.* (*d*) *Absorption, Demulcents, Excretion, Decomposition, Idiosyncrasy* (Ex. 24 to 28, inclusive). (*e*) Study of Materia Medica, Tannins and Vegetable Astringents, Lesson 7.	Two to Three.
(*f*) Reports, Conference and Recitation on Ex. 24 to 28, inclusive.	One.
(*g*) *Treatment of Poisoning* (Ex. 29). (*h*) Study of Materia Medica, Lesson 8.	Two to Three.
Twenty-first Week:	
(*a*) Recitation on Metals and Astringents (p. 681 to 693; and Materia Medica, Lessons 7 and 8.	One.

	HOURS.
(*b*) *Emetics* (Ex. 30); *Gastroenteritis* (Ex. 32); *Glycosuria* (Ex. 34); *Convulsants and Depressants, Mammals* (Ex. 39 and 40). (*c*) Study of Materia Medica, Hysteric Sedatives and Rubefacient Oils, Lesson 9.	Two to Three.
(*d*) Reports, Conference, and Recitation on Treatment of Poisoning (Ex. 29; Ex. 14; Ex. 18 C; Ch. VI, p. 88 to 92). (*e*) Recitation on Summaries 1 to 3 (Ch. XXXVIII).	One.
(*f*) *Convulsants and Depressants on Frogs* (Ex. 37 and 38, 41 to 44).	Two to Three.
Twenty-second Week:	
(*a*) Recitation of Volatile Irritants to Rubefacient Oils, inclusive (p. 694 to 698 and Lesson 9). (*b*) Reports, Conference, and Recitation on Ex. 30 to 36, inclusive. (*c*) Recitation on Summary 4.	One.
(*d*) *Muscle* (Ex. 45). (*e*) Study of Materia Medica, Stimulants for Ulcers and Urinary Disinfectants, Lesson 10.	Two to Three.
(*f*) Reports, Conference, and Recitation on Convulsants and Depressants (Ex. 37 to 44, inclus.). (*g*) Recitation on Summaries 5 to 10.	One.
(*h*) Test on Prescription Writing. (*i*) *Salt and Ion Actions* (Ex. 46).	Two to Three.
Twenty-third Week:	
(*a*) Recitation on Ulcer Stimulants and Urinary Antiseptics (p. 699 to 701; and Lesson 10). (*b*) Reports, Conference, and Recitation on Muscle, Osmosis, and Ion Action (Ex. 45 and 47). (*c*) Recitation on Summary 12.	One.
(*d*) *Heart* (Ex. 48 and 49). (*e*) Study of Materia Medica, Diuretic Oils and Bronchial Stimulants, Lesson 11.	Two to Three.
(*f*) Recitation on Heart (Ex. 48).	One.
(*g*) *Cardiac Nerves, Blood Vessels, Pulse, Artificial Circulation* (Ex. 50 to 53).	Two to Three.
Twenty-fourth Week:	
(*a*) Recitation on Diuretic Oils and Bronchial Stimulants (p. 701 to 703; and Lesson 11). (*b*) Reports, Conference, and Recitation on Heart and Circulation (Ex. 49 to 53).	One.

	Hours.
(*c*) *Pupils, Glands, Back-Work* (Ex. 54 and 55).	Two to Three.
(*d*) Study of Materia Medica, Toxic Oils to Cantharidin Group, inclusive, Lesson 12.	
(*e*) Incompleted Laboratory Reports.	One.
(*f*) Recitation on Summaries 13 and 25.	
(*g*) Review of Summaries No. 1 to 12.	
(*h*) Reports, Conference, and Recitation on Ex. 54 and 55.	Two to Three.
(*i*) *Demonstration of Herbarium Specimens for Ch. XXIX.*	
(*k*) *Assignment of Lockers* (*Operative Work*).	
Twenty-fifth Week:	
(*a*) Recitation on Ch. XXIX to Physical Irritants (p. 703 to 710, and Materia Medica, Lesson 12).	One.
(*b*) Recitation Summary 14.	
(*c*) *Ex. 56 to 59, inclusive.*	Two to Three.
(*d*) Study of Materia Medica, Stomachics, Lesson 14.	
(*e*) Recitation on p. 710 to 719; and Lesson 13.	One.
(*f*) *Optional Experiments or Arrangement of Notes.*	Two to Three.
Twenty-sixth Week:	
(*a*) Recitation on Stomachics (Ch. XXX, p. 719 to 725; and Lesson 14).	One.
(*b*) Reports, Conference, and Recitation on Ex. 56 to 59, inclusive.	
(*e*) *Ex. 60 to 63, inclusive.*	Two to Three.
(*d*) Study of Materia Medica, Carminatives, Lesson 15.	
(*e*) Written Test and Specimens, Ch. XXVIII and XXIX, p. 660 to 719.	One.
(*f*) Prescription Writing and *Optional.*	Two to Three.
Twenty-seventh Week:	
(*a*) Discussion of Test.	One.
(*b*) Reports, Conference, and Recitation, on Ex. 60 to 63.	
(*c*) Recitation on Summaries 15 to 17.	
(*d*) *Ex. 64 to 67.*	Two to Three.
(*e*) Study of Materia Medica, Cathartic Oils and Anthracene Derivatives, Lesson 16.	

	HOURS.
(*f*) Recitation on Carminatives (Ch. XXX, p. 725 to 726; and Lesson 15.	One.
(*g*) *Optional.*	Two to Three.
Twenty-eighth Week:	
(*a*) Reports, Conference, and Recitation on Ex. 64 to 67. (*b*) Recitation on Summaries 18 to 26.	One.
(*c*) *Ex. 68 to 73.* (*d*) Study of Materia Medica, Anhydrid Cathartics, Lesson 17.	Two to Three.
(*e*) Recitation on Cathartic Oils and Anthracene Derivatives (Ch. XXX, p. 726 to 732; and Lesson 16).	One.
(*f*) *Optional.*	Two to Three.
Twenty-ninth Week:	
(*a*) Reports, Conference, and Recitation on Ex. 68 to 73. (*b*) Recitation on Summaries 23 to 31.	One.
(*c*) *Ex. 74 to 76.* (*d*) Study of Materia Medica, Anthelmintics, Lesson 18.	Two to Three.
(*e*) Recitation on Anhydrid Cathartics (Ch. XXX, p. 732 to 735; and Lesson 17). (*f*) Recitation on Summary and Uses of Cathartics (Ch. XXX, p. 735 to 742).	One.
(*g*) *Optional.*	Two to Three.
Thirtieth Week:	
(*a*) Reports, Conference, and Recitation of Ex. 74 to 76. (*b*) Recitation on Summaries 32 to 39.	One.
(*c*) *Demonstration of Herbarium Specimens of Native Poison Plants.*	Two to Three.
(*d*) Recitation on Anthelmintics (Ch. XXX, p. 742 to 746; and Lesson 18). (*e*) Recitation on Summaries 40 to 46.	One.
(*f*) Review Quiz on Summaries. (*g*) Prescription Writing.	Two to Three.

Written and practical test on the laboratory work.

THE LABORATORY ROOMS.

The pharmacology courses may be given in the chemic, pharmaceutic, and physiologic laboratories, if no other arrangement can be made; but the efficiency of the teaching and research is undoubtedly enhanced by separate rooms and equipment. The laboratory should consist of a chemic and animal department, preferably in adjacent rooms. The materia medica collection may be placed in the chemical room, or in a convenient corridor. Additional rooms for lectures, research, toxicology, storage, for the keeping and observation of animals, etc., are highly desirable. They should be in close vicinity; the animal rooms, however, will be less annoying in another part of the building.

EQUIPMENT OF THE CHEMICAL DEPARTMENT.

This should contain the chemic tables, lockers, and sinks for the students; a fume-chamber; balance and druggists' scales; and a moderate equipment of chemic apparatus.

The **chemic tables** may be of any of the varieties used in chemic laboratories. A height of three feet is convenient. A working-space of 6 by 2 feet, and a single locker, suffices for each pair of students. The lockers should be of the height of the table, 2½ feet wide, with a shelf nine inches from the top. It is cheap and convenient to have quarter-inch iron rods fixed to the tops of the tables, for clamping retort rings, etc.

TABLE XVII.—EQUIPMENT OF EACH CHEMIC LOCKER

(for two students).

Only the more common apparatus need be placed in the lockers, additional pieces being placed on the tables or assigned on written requisition, when needed. A list of these is furnished with each exercise:

1	Bunsen burner and tube.
1	Retort stand.
2	Retort-rings.
1	Tripod.
1	Liter wash bottle.
2	Evaporating dishes (10 cm.).
1	Evaporating dish (400 c.c.).
2	Funnels, 6 cm.
1	Funnel, 12 cm.
5	Beakers, 25-150 c.c.
4	Flasks, 250 c.c.
2	Tumblers.
30	Test-tubes.
2	Test-tube racks.
2	Test-tube brushes.
2	Test-tube clamps.
2	Slide clamps.
1	Mortar and pestle, 10 cm.
1	Pill tile.
1	Pill-box.
1	Powder box.
1	Steel spatula.
1	Horn spatula.
1	Thermometer, 0-100.
1	25 c.c. Conic graduate.
6	Watch glasses, 1½ inch.
1	Sponge.
1	Towel.

Filter paper; label paper; wire gauze; glass slides, tubing, rods, pipettes, etc. Broken evaporating dishes.

TABLE XVIII.—SPECIAL CHEMIC APPARATUS.

For twelve students; to be assigned as needed.

2 Microscopes (cheap model, low power).
4 Separatory Funnels (150-500 c. c.).
3 Spectroscopes.
3 Waterbaths.
2 Liebig stills.
1 Army and Navy scale and metric weights.

TABLE XIX.—SPECIAL CHEMIC APPARATUS FOR DEMONSTRATION AND RESEARCH.

The equipment for these purposes depends on the resources of the establishment, the special investigations pursued, etc. The following will be found well-nigh indispensable:

Flasks, Funnels, Beakers, Evaporating Dishes, etc.; Glass rods and tubing, Rubber, etc.; Corks; Burners; Stands; Clamps; Burettes, Pipettes, Graduates, etc.; Spatulas, Percolators, Dialyzers, etc.; Porcelain-mortars, 15 and 20 cm.; Iron Mortar; Desiccators; Crucibles and Tongs; Mechanics' and Carpenters' Tools; 6 Fermentation Tubes; Centrifuge; Vacuum Pump; Beckmann's Apparatus; Ovens for 40 and 100° C.; Thermometers; Combustion Oven; Analytic Balance and Weights; Platinum; Polarimeter; Glass-blower Bellows; etc., etc.

Reagents for Chemical Work.— The reagents employed in pharmacology are so numerous, that the problem of keeping them conveniently accessible is quite serious. It will be found convenient to divide them into three classes; (A) for every three students; (B), for every six students; and (C), for every twelve students, for special experiments. (A) and (B) should be arranged in alphabetic order on the shelves of the chemic tables. (C) may be arranged by the exercise numbers, and kept on a side-shelf when not in use.

It will be found very advantageous to number the containers and their places, and to demand that every reagent be replaced in proper order as soon as used.

A number of the solutions are perishable and should not be kept over a year. These are marked * in the following lists. Others (**) should be furnished fresh for each exercise. It is well to distinguish these by colored labels (green for * and red for **) for the ready guidance of the laboratory assistant. He can save himself some labor by keeping concentrated stock solutions on a special shelf.

TABLE XX.—LIST A.—COMMON CHEMIC REAGENTS.

Kept on shelves of chemic tables. 50 to 100 c. c. of each. For three students.

Acid Acetic, 5%.
“ Hydrochloric, Conc., C.P.
“ “ 5%.
“ Nitric, Conc., C.P.
“ Picric, Saturated aqueous.
“ Sulphuric, Conc., C.P.
“ “ 5%.
Alcohol, Ethyl, 95%.
Ammonia Water, 10%.
Ammonium Sulphate, Powdered.
Barium Chlorid, 5%.
“ Hydrate, Saturated Aqueous.
** Bromin Water, Saturated Aqueous.
Calcium Chlorid, 1%.
“ Hydrate (Lime Water), Saturated Aqueous.

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*(Green Label) Should not be kept over a year.
** (Red Label) Should be freshly made.

Chloroform.
Cupric Sulphate, 5%.
Ether.
Ferric Chlorid, 10%.
*Ferrous Sulphate, 1%.
Glycerin.
Iodin in KI, 1% of iodin, KI q. s. to dissolve.
Lead Acetate, 5%.
Litmus Paper.
Magnesia Mixture.[1]
Magnesium Sulphate, powdered.
Mercuric Chlorid, 1%.
Mercuric-Potassic Iodid (Mayer's Reagent).[2]
Oleum Olivæ or Gossypii (cottonseed).
Potassic Bichromate, Saturated (about 3½%).
Potassic Iodid, 3%.
“ Ferricyanid, 5%.
“ Ferrocyanid, 5%.
Silver Nitrate, 1%.
Sodium Acetate, 5%.
“ Carbonate, 5%.
“ Chlorid, crystals.
“ Hydrate, 10%.
“ Phosphate, 5%.
“ Sulphate, powdered.

TABLE XXI.—LIST B.—LESS COMMON CHEMIC REAGENTS.

On top shelf of chemic tables. For six students:

	Gram or c.c. (about).
Acacia, Granulated	20
“ Mucilage (33%)	25
Acetanilid	20
Ac. Carbol. Liq.	25
“ “ 5%	25
* “ “ 0.3%	25
“ Gallic	1
“ Phosphotungstic (10% in 4% HCl.)	10
“ Tartaric	10
Alcohol, 5%	25
Antipyrin, 10%	10
Apomorphin Hydrochlorid	0.1
“ 1 : 500	25
Atropin Sulphate	0.1
Bismuth Subcarb.	20
Brucin	0.1
Caffein, Citrated	1.
Calomel	10.
Camphor, Spirits	25
Chloral	5
Cinchona Infusion (5% in 20% alcohol.)	25
Cinchona, Tr.	25
Cocain Hydrochlorid	0.1
Codein	0.1
Digitalin	0.1
Excipient	10.
Ferric Chlorid, Tr.	50.
Gasolin	50
Glycyrrhiza, Pv.	25
*Guaiac, Tr.	10
Iodin, 1% alcoholic	10
Lead Subacetate, Solution	25
Methyl Alcohol	25
Millon's Reagent[3]	25
Morphin Sulph.	1.1
“ “ 2% aqueous.	10.
Nux Vomica, Pd.	1.
Phenacetin	5.
Picrotoxin	0.1
Pot. Bichrom. Pd.	5.
“ Bromid, Sat.'d	25
“ Chlorate	10
“ Chlorate, Sat.'d	25
* “ Cyanid, 1%	25

[1] *Magnesia Mixture:*

$MgSO_4$ Crystals	1
NH_4Cl	1
NH_3 (10%)	4
Water	8

[2] *Mersuric-Potassic Iodid (Mayer's Reagent):*

$HgCl_2$	13.55 Gm.
KI	49.8 Gm.
Water	q. s. 1 Liter.

[3] *Millon's Reagent:* Dissolve 1 part of metallic mercury in 1 part by weight of cold fuming nitric acid, cool, and dilute with two parts of distilled water. Decant from the sediment. The solution contains mercuric and mercurous nitrate.

	GRAM OR C.C. (about).
Pot. Nitrate, pd.	10
“ Oxalate, 2%	25
“ Permang., 1%	25
Quin. Sulph., dry	0.1
“ “ 0.1% aqueous. (acidulated.)	25.
“ “ Sat. Aq.	25
Resin, coarse powder	10
Resorcin	0.5
Rhubarb Infusion (5% in 25% alcohol.)	25.
Salicin	1.
Salol	1.
Sand	100.
Santonin	0.5
Soap Bark, Tr.	25.
Sod. Acetate	10.
“ Benzoate	10
“ Benzoate, 5%	25

	GRAM OR C.C. (about).
Sod. Bicarb.	20
“ Borate, 5%	25
“ Chlorid, Sat.'d	25
“ Hyposulphite, 1%	25
“ Nitrite, pd.	10
“ Nitrite, 10%	20
“ Salicylate	5
“ Sulphate, 1%	25
Spir. Æther. Nitrosi	20
Starch	25
Strychnin Sulph.	0.1
“ “ 1%	10.
Sugar, Cane	25
Tannin	1.
Turmeric Paper	..
Turpentine	25
Uva Ursi, Infusion (5% in 20% alcohol.)	25
Veratrin	0.1

TABLE XXII.—LIST C.—SPECIAL CHEMIC REAGENTS.

For twelve students; on side shelf; arranged by exercises.

The number of the exercise may be placed on the label: * = green label; ** = red label.

	GM. OR C.C.
Exercise 3:	
**Tannin, 1%	50
Metallic Sodium (25 small pieces, in petroleum)	—
Quinolin	5
Morphin Sulph., 2%	5
Nicotin, 0.1%	5
Atropin Sulph., 1%	5
Strychnin Sulph., 1%	5
* Salicin, 1%	50
* Gallic Acid, 1%	50
* Acacia, 10% (made by heat)	50
* Lettuce, Tinct.	25
Curcuma, Tinct., 1% (in 25% alcohol.)	25
Boric Acid, 5%	100
Cochineal	5
Tr. Persionis	5
Exercise 7:	
NaCl	20
Saccharum	100
**Infus. Menth. Pip.	300
Calomel	20
Starch (Amylum)	100
Cod Liver Oil (Ol. Morrhuæ)	100
Granulated Acacia	30

	GM. OR C.C.
Petrolatum	150
Emplastrum	50
Pv. Glycyrrhizæ	30
Exercise 8:	
Chlorate of Potash and Tannin Mixture.	
* Hydrogen peroxid	50
**Albumin (one egg white in 100 c.c. water, strained)	100
* Liquor Pepsini	50
* Misturæ Cretæ	50
Exercise 10; No. 1—7:	
Morphin Sulphate, 0.1%	50
* Sod. Iodate, 1%	10
**2% Starch Paste	50
* Strychnin Sulph. 1 : 50,000.	50
* Marquis' Reagent	10
Ammon. Molybdate	1
No. 8—14:	
* Cocain, 1%	10
**Adrenalin, 1 : 50,000 or dilute suprarenal extract.	10
* KOH, small dry fragments	20
* Picrotoxin, 1 : 1,000	10
No. 15—31:	
* Calx chlorata (test efficiency)	5

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[1] Exercise 31.

	GM. OR C.C.
* HCN, 0.1%	50
Copper foil, small pieces	20
Fowler's Solution	50
Phosphorus in small pieces	20
No. 33:	
* 1% Cane Sugar	100
* 10% Lactose	100
* 10% Glucose	100
* 10% Levulose	100
10% Glycerin	100
* 0.01% Saccharin	100
Exercise 13:	
Drugs for students (at preceding laboratory day).	
**2% Starch Paste	100
Exercise 14:	
**10% Decoction of Tea	50
**10% Decoction of Coffee	50
**Albumin Solution (one egg white to 100 c.c. water, strained)	50
Exercise 15:	
**Albumin Solution	400
**Defibrinated Blood	400

	GM. OR C.C.
Exercise 16:	
1% Caffein	10
Exercise 17:	
Alcoholic Methylen Blue	10
Tr. Iodin	10
Cerate Cantharides	10
25% Croton Oil	10
Tartar Emetic Ointment (10%)	10
Veratrin in Starch, 1 : 500.	1
Soap-bark	—
Aconite, 1%	10
Alum, 5%	25
Exercise 21:	
**Diluted Blood, 4%	200
* Fresh Ammon. Sulphid	25
Phenyhydrazin	10
* Pyrogallol, 10%	10
* HCN, 2%	10
Exercise 22:	
**Defibrinated Blood	20
Solutions of the experiment.	
Exercise 23:	
See Exercise.	

EQUIPMENT OF THE ANIMAL DEPARTMENT.

This should be equipped with a large demonstration-table and case of demonstration apparatus; sinks; easily movable tables and lockers for students' work; shelves for reagents; a chemic bench; drawers for supplies, etc.

Tables for Animal Work.—These may be of pine, strongly built, 3 feet high by 6 feet long and 2 feet wide; 1½ inch top; solid legs. Drawers are rather objectionable. Two tables are needed for six students. In operative experiments the two tables are set in the form of a T, the lower table being used for operating, the upper for apparatus.

The lockers (one for six students) may be placed at the side of the room, near the tables. There should also be an open shelf for special apparatus.

Apparatus.—It is advisable to buy as much as possible of manufactured apparatus, of the best quality which the resources will allow.[1] The satisfaction of working with instruments which give accurate and trustworthy results; the training in exactness; and the practice with apparatus such as would actually be used in research; are advantages which offset, in most cases, those of home-made apparatus. The latter, however, have some valuable qualifications besides cheapness; especially in that they encourage independence and ingenuity. A certain amount of home-made apparatus is therefore very useful, especially if time permits the students to manufacture it themselves. Some directions for this are given in Chapter XXXIV, and many more can be devised by the exercise of a little inventive talent.

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[1] A very good quality of physiological apparatus can be obtained at a very reasonable price from the Harvard Apparatus Company, 47 Pearl St., Brookline, Mass. Research apparatus may be obtained from C. F. Palmer, 6 Upper Tulse Hill, London, S. W. It is rather advantageous to familiarize the students with several types and makes of apparatus.

* Green label. ** Red label.

The following physiologic apparatus will be indispensable for the course as outlined:

TABLE XXIII.—LIST OF APPARATUS IN LOCKERS AT BEGINNING OF COURSE.

(For six students.)

See next table for explanation of †.

† 1 Battery, key, induction coil and electrodes.
2 Beakers, small size.
1 Bunsen burner and tube.
2 Camel's hair brushes.
† 5 Cannulæ, assorted sizes, for vessels, in box.
2 Cork-boards, plain.
2 Evaporating dishes.
2 Flasks, 250 c.c.
† 1 Funnel, 6 cm.
2 Glass-rods.
† 2 Graduates, 25 c.c., conic.
† 1 Saucepan.
† 1 Bundle ligatures, fine.
† 1 Bundle ligatures, coarse.
400 c.c. Normal Saline Solution, 0.75%.
† 400 c.c. Normal Saline Solution, 0.9%.
1 Cork of pins.
2 Pipettes, plain.
3 Pipettes, graduated in ¼ c.c.
2x2 inches Fine Sand Paper.
1 Sealing Wax.
† 2 Sponges.
10 Test-tubes.
1 Test-tube rack.
1 Test-tube brush.
† 2 Towels.
1 Tripod and gauze.
† 2 Tumblers.
2 Wires for pithing.
† 1 Box of Labels.

TABLE XXIV.—LIST OF ADDITIONAL APPARATUS, PLACED IN THE LOCKERS WHEN THE OPERATIVE WORK ON MAMMALS BEGINS.

(For six students.)

This, and the pieces marked † in Table XXIII, should be placed in shallow boxes, which can be easily brought to the operating table:

2 Tracheal Cannulæ.
3 Ureter Cannulæ.
1 Aortic Cannulæ.
2 Feathers.
1 Large pipette for filling manometer.
3 Mohr's Clamps.
15 c.c. Hypodermic Syringe and large needle.
1 Screw Clamp.
200 c.c. of 25% $MgSO_4$.
200 c.c. of Ether (or A. C. E. Mixture).
100 c.c. of 50% Glycerin (wide-mouthed bottle).
1 Woulf's bottle, 2 neck, 250 c.c.
3 Bull-dog forceps.
1 Hemostat.
2 Aneurism needles.
1 Suture needle.
1 Set of Ropes.

This apparatus is again removed from the lockers at the end of the course.

TABLE XXV.—LIST OF LARGER APPARATUS FOR OPERATIVE WORK.

(For six students.)

This apparatus should be kept on the tables, or on conveniently accessible shelves. The pieces should be mounted on stands, for immediate use:

1 Dog board.
1 Bellows, arranged for artificial respiration.
1 Brodie bellows.
1 Muscle-lever, arranged for myocardiagram.
1 Ingestion burette (50 c.c., graduated in ${}^{1}/_{10}$).
1 Rabbit-board.
1 Mercury manometer.
2 Kymographs.
1 T-piece for respiration.
1 Bellows — Respiration recorder.
1 Signal magnet, with key and battery.
1 Pipette, 10 c.c. (graduated in ${}^{1}/_{10}$).

Of the following pieces, one will answer for two or three sets:

Oncometer.
Vein-Manometer.
Pneumograph Receiving Tambour (Brodie's or Marey's).

TABLE XXVI.—APPARATUS ASSIGNED ON OCCASION AND NEEDED FOR DEMONSTRATIONS (in addition to that in Tables XXIII to XXV).

(36 Students.)

6 Stomach-catheters (English, No. 10).
6 Feeding-bulbs.
H_2S apparatus.
6 Clinical thermometers, centigrade.
4 Mouth-gags.
3 Catheters.
2 Dog cages.
3 Rabbit cages.
Large bell jar (for cat or rabbit).
6 Small (Liter) bell jar, open neck (for frogs).
6 Induction coils with batteries, electrodes, and key.
6 Additional dry cells.
12 Muscle levers and 10 Gm. weights.
6 Maximal-load springs.
4-250 c.c. Aspirator bottles.
3 Artificial circulation models.
12–1L. "Mercury Bulbs" for perfusion apparatus.
2 Smoking arrangements for drums.
1 Varnish trough.
3 Files.
Operating instruments.
Ergograph.
Plethysmograph.
Sphygmomanometer.
Sphygmograph.
Gas-chamber.
Muscle-heater.
1 Spool Linen Thread (No. 50).
1 Spool Silk (Buttonhole twist).
1 Ball Cotton wrapping twine.
1 Ball Express twine (Dauntless flax, No. 24).
1 Ball Rope (India hemp, No. 3).
1 Large water-bath.
12 Mohr's clamps.
6 Screw clamps.
6 T and Y pieces, sizes 5 and 7.
1 Hot-water funnel.
5 Fine forceps.
5 Fine curved scissors.
3 6-inch curved (hair) scissors.
2 Spring scales for animals.
3 Thermometers, 1-100° C.

The following materials should be in *drawers* conveniently accessible to students: Wire of all kinds; straws for levers; sealing wax; filter paper; glass and rubber-tubing.

TABLE XXVII.—ANIMALS NEEDED FOR LABORATORY COURSE.

The course as outlined in Chapters III to V requires the following animals, for a class of 30 to 36 students: 1 gross Frogs (medium); 18 Turtles; 1 Rooster; 2 Guinea-pigs; 20 Medium rabbits; 25 Dogs (small) or Cats.

For every six students below 36, the following may be subtracted: Frogs, 17; Turtles, 3; Rabbits, 2; Dogs, 4.

TABLE XXVIII.—SOLUTIONS NEEDED IN THE ANIMAL WORK.

In the following list, the number of bottles needed for a class of 36 precedes the name; the last figure indicating the quantity (c. c.) in each bottle. (Solutions which do not spoil may be made up in three or five times this amount.) (0.75) and (0.9) indicates that the drug is to be dissolved in this strength of sodium chlorid. (110) means that the salt is to be dried at 110° C. The bottles are to be arranged alphabetically, except when the quantity exceeds 400 c. c. The saline bottles should be supplied with a siphon. The significance of * and ** is given on page 781. Hypodermic tablets may be used to make small amounts of very perishable solutions:

			c. c.
	1	Acid Acetic, 5%	50
*	1	“ Citric, 1%	50
* *	1	“ Citric, 1% in 10% starch paste	50
	1	“ Hydrochloric, $^{1}/_{10}$%	50
* *	1	“ Hydrochloric, $^{1}/_{10}$% in 25% acacia	25
*	3	“ Hydrocyanic, 2%	10
	1	Aconite, Tablets, 0.3 c. c. of 10% tinct	35
	3	“ 10% tinct.	50
*	3	“ 4% infus. (0.75)	10
	3	Adrenalin, 1 : 1,000	10
* *	3	“ 1 : 10,000 (0.9)	15
*	1	Agurin, 5%	20
	3	Alcohol, 95%	50
	2	“ 50%	30
	2	Ammonia, 10%	10
	3	Ammonium Chlorid, 1%	400
	3	Amyl Nitrite	10
	1	“ “ 3 drop pearls	35
	3	Anesthetic (A. C. E., equal parts)	250
*	1	Apomorphin Hydrochlorid, 1%	10
* *	1	Aspidium, 5% infusion	25
	1	Atropin Sulphate, 1 mg. tablets	35
	3	“ “ 1% (0.75)	20
*	3	“ “ $^{1}/_{10}$% (0.75)	10
	3	Barium Chlorid, 1%	100
	3	“ “ $^{1}/_{10}$%	25
	1	“ “ 0.24% (110)	100

* Green label. ** Red label.

	3	Caffein, 1%	50
*	3	“ 0.1%	25
*	3	“ 0.01%	25
*	3	“ 1 : 5,000	15
	1	Calcium Chlorid (110), 0.15% (0.9)	100
	1	“ “ (110), 16.33 Gm. to 1 Liter	—
	1	Calomel	25
	3	Camphor, saturated (0.75)	25
	1	“ 20% in oil	25
	1	Cannabis Indica, F.E.[1]	20
*	3	Chloral, 10%	25
*	3	“ 1%	10
	3	Chloroform	100
*	3	“ saturated solution (0.75)	25
* *	3	Cocain hydrochlorid, 1%	10
	1	“ “ 10 mg. hypoderm. tablets	25
	1	Colchicin, F.E., Root and Seed	15
	2	Copper Sulphate, 1%	50
*	3	Curare, ½% (0.75)[2]	50
* *	3	“ $^{1}/_{10}$% (0.75)	20
	3	Digitalis, 10% tinct.	25
* *	1	“ 20% infus. (0.75)	5
* *	1	“ 10% infus. (0.75)	5
* *	3	“ 4% infus. (0.75)	100
* *	3	“ 1% infus. (0.9)	15
* *	1	“ ⅕% infus. (0.9)	25
	1	“ tablets, 0.3 c. c. tinct.	35
*	1	Dionin, 10%	1
* *	3	Diuretin, 5%	25
	1	Ergot, F.E.	10
* *	3	“ 2% (0.9)	50
	3	Ether	100
*	3	“ saturated solution (0.75)	10
	1	Ethyl Chlorid tube	—
*	3	Eucain, 1%	5
*	3	Heroin hydrochlorid, $^{1}/_{10}$%	10
*	1	Hydrastinin hydrochlorid, $^{1}/_{10}$%	30
* *	1	Hydrastis, F. E. 2% (0.9)	50
	1	Gasolin	50
	3	Gréhants' Anesthetic (page 802)	400
	1	Lead Acetate papers	—
	1	Litmus Papers	—
	1	Locke's Fluid	7,000
	2	Machine Oil	25
	1	Magnesium Chlorid (110), 0.19% (0.9)	100
	3	“ Sulphate (110), 3.6% [cryst. 7.5%]	100
	1	“ “ 25% crystals	100
	1	Mercuric Chlorid, $^{1}/_{10}$%	50
*	3	Morphin Sulphate or Hydrochlorid, 4%	100
*		“ “ “ “ 1%	10
* *	1	Muscarin Nitrate, $^{1}/_{10}$% (0.75)	10
	1	Nicotin	1
*	3	“ 1% (0.75)	20
* *	2	“ ⅕% (0.75)	20

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[1] F. E. stands for fluidextract.

[2] *Permanent Suprarenal Extract:* Macerate for three days 10 parts of fresh or 4 of dried, suprarenal in a mixture of 1 part of boric acid, 2 glycerin, 2 alcohol and 6 water. Filter. This may be used like the 1:1000 adrenalin solution.

* Green label. ** Red label.

* *	3	" $^1/_{10}$% (0.75)	50
	1	Orthoform	5
	3	Petrolatum	20
*	3	Phenol, 1% (0.9)	100
	1	Phlorrhizin	5
	1	Physostigmin Salicylate, 1 mg. hypodermic tube	25
* *	1	" " 1% (0.75)	2
* *	3	" " $^1/_{10}$% (0.75)	5
*	1	Picrotoxin, 1 : 250	5
	1	Pilocarpin hydrochlorid, 1 mg. hypoderm. tube	25
*	1	" " 1% (0.75)	10
*	3	" " $^1/_{10}$% (0.75)	30
	1	Potassium Chlorid, crystals	10
	1	" " 9%	25
	3	" " 1%	100
	3	" " $^1/_{100}$%	25
	1	" Iodid, 1%	50
	2	" Permanganate, 1%	100
* *	1	Quassia, 5% infus.	25
*	3	Quinin Hydrochlorid, 1% (0.75)	25
*	3	" " $^1/_{10}$% (0.75)	25
* *	3	" " $^1/_{100}$% (0.75)	25
*	3	" " $^1/_{10}$% (0.75), plus 10% F.E. Yerba Santa	10
	2	Ringer's Fluid	400
	1	Santonin, $^1/_{10}$% (with NaOH)	25
* *	2	Saponin, $^1/_{10}$% (0.75)	20
	1	Sod. Arsenate, 5%	10
	3	" " 1% (0.9)	100
	3	Sodium Chlorid, crystals	5
	2	" " 10%	25
	3	" " 5%	2,000
	3	" " 2%	2,000
	5	" " 1%	2,000
	1	" " 0.9%	4,000
	1	" " 0.75%	4,000
	1	" Citrate, (110) 27.37 gm. to 1 Liter	—
	2	" Fluorid 0.43% (isotonic with 0.6% NaCl)	30
	2	" Nitrite, 10%	25
	3	" Nitrite, 1%	10
	3	" Sulphate (110), 2.5%	400
	3	" " (110), 2%	1,000
	3	" " (110), 1.9%	100
* *	1	Strophanthus, $^1/_{10}$% (0.9)	100
	3	Suprarenal Extract in 50% Glycerin[1]	25
*	1	Strychnin Sulphate, 1% (0.75)	25
* *	3	" " $^1/_{10}$% (0.75)	50
* *	3	" " $^1/_{50}$% (0.75)	15
* *	3	" " $^1/_{100}$% (0.75)	20
* *	1	" " $^1/_{10}$% in 25% acacia	5
*	3	Sugar, Cane, 10%	25
* *	1	Theocin, 5%	10
*	1	Turpentine Emulsion, 1%	25
* *	1	Urea, 1.9%	100
*	3	Urethane, 20%	20
*	3	Veratrin Sulphate, 1%	50

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[1] The addition of a little thymol will improve the keeping quality of curare solution, without interfering with its action.

* Green label. ** Red label.

* 3 " " $^1/_{10}$%	5
1 Yohimbin Tablets, 5 mg.	10
2 Zinc Sulphate, 1%	50

TABLE XXIX.—ASSIGNMENT OF OPERATIVE WORK.

To avoid confusion, the students in each set should be assigned a definite portion of the work, as follows:

Place I.—Weigh the animal; give anesthetics (page 801) and injections (page 803); attend to artificial respiration (page 817); cleaning.

Place II.—Blood-pressure tracing and pulse (page 811, 814).

Place III.—Operate (pages 807 to 811) and record. Observations and tracings other than blood-pressure (Respiration, page 815, etc.).

The students of each place set up their apparatus. As much as possible should be prepared in advance. Each set will see that its tables are left neat and clean at the end of the exercise.

The assignment of the students to these places is given in each exercise. The following may serve for orientation (the students of each set being numbered from A to F):

Exercise.	Pl. I.	II.	III.	Exercise.	Pl. I.	II.	III.
58	AB	CD	EF	65	EF	AB	CD
59	CD	EF	AB	67	AB	CD	EF
61	EF	AB	CD	69 to 73	CD	EF	AB
62	AB	CD	EF	74	EF	AB	CD
63	CD	EF	AB	75	AB	CD	EF
				76	CD	EF	AB

The exercises which are bracketed are assigned to different sets on the same day.

TABLE XXX.—TEXT-BOOKS OF EXPERIMENTAL PHARMACOLOGY AND PHYSIOLOGY.

Those marked with an asterisk are referred to in the text. The others are useful, and indeed indispensable for advanced work; but they will not be needed in the regular course:

*Beddard, Edkins, Hill, MacLeod, and Pembrey: *Practical Physiology;* Edw. Arnold, London (1902).

Binz: *Vorlesungen über Pharmacologie;* Hirschwald, Berlin (1891).

*Brodie: *Essentials of Experimental Physiology;* Longmans, Green & Co., London, New York, and Bombay (1898).

Brunton: *Pharmacology, Therapeutics, and Materia Medica;* Lea Bros., Philadelphia (1885).

Cyon: *Methodik;* Ricker, Giessen and St. Petersburg (1876).

Dubois: *Physiologie Expérimentale;* Carré et Naud, Paris (1900).

*Edmunds and Cushny: *Laboratory Guide in Experimental Pharmacology;* Wahr, Ann Arbor, Mich. (1905).

*C. W. Greeme: *Experimental Pharmacology;* Columbia, Missouri (1905).

Hall: *Laboratory Guide in Physiology;* Chicago Med. Book Co. (1897).

*The Harvard Apparatus Company Catalogue; 47 Pearl Str., Brookline, Mass.

Heinz: *Handbuch der experiment. Pathol. u. Pharmakologie;* Fischer, Jena (1904).

Hermann: *Physiologisches Practicum:* Vogel, Leipzig (1898).
Hermann: *Experimentelle Toxicologie;* Hirschwald, Berlin (1874).
Kobert: *Lehrbuch der Intoxicationen;* Enke, Stuttgart (1902).
Miller: *Experimental Pharmacology;* Northwestern University Medical School, Chicago (1904).
Pembrey and Phillips: *Physiological Action of Drugs;* Arnold, London (1901).
Sanderson and others: *Handbook for the Physiological Laboratory;* Lindsay & Blakiston, Philadelphia (1873).
Schäfer: *Practical Physiology,* Longmans, Green & Co., London, New York, and Bombay (1901).
* Stewart: *Manual of Physiology,* Saunders, Philadelphia (1905).

TABLE XXXI.—TEXT-BOOKS OF PHARMACOLOGY.

Cushny: *Pharmacology and Therapeutics,* Lea Bros., Philadelphia (1903).
Von Hofmann: *Atlas of Legal Medicine,* Saunders, Philadelphia.
Schmiedeberg: *Pharmakologie,* Vogel, Leipzig (1902).
* Sollmann: *Text-Book of Pharmacology,* Saunders, Philadelphia.
White (Editor): *Text-Book of Pharmacology and Therapeutics,* Pentland, Edinburgh and London (1901).
Wood: *Therapeutics,* Lippincott (1902).

TABLE XXXII.—REFERENCE WORKS FOR CHEMICAL AND PHARMACEUTICAL WORK.

Dispensatory, National or United States:
Flueckiger: *Reactions,* Davis, Detroit.
Hager: *Handbuch der Pharmaceutischen Praxis,* Springer, Berlin.
* Hatcher and Sollmann: *Text-Book of Materia Medica,* Saunders & Co. (1904).
Remington: *Practice of Pharmacy,* Blakiston, Philadelphia.
Schaer and Zenetti: *Analytisch-chemische Uebungsarbeiten,* Gaertner, Berlin (1897).
Holland: *Medical Chemistry and Toxicology,* Saunders, Philadelphia.
* *United States Pharmacopœia,* Eighth Revision, Blakiston, Philadelphia.

Cost on Installation.—This depends greatly on circumstances. It may be made very moderate if the resources of other departments are utilized (although this is not true economy in the end). The contents of the chemic lockers cost about $6 to $7 (for two men); those of the animal lockers about $15 (for six men). The chemicals require about $100. A thorough equipment requires a much larger sum.

Cost of Maintenance.—This again depends entirely upon circumstances. For a class of 36 men, the animals will cost about $30 to $50, the chemicals $25 to $40 per year. An independent or research department will have many other expenses.

CHAPTER XXXIV.

EXPERIMENTAL TECHNIC AND APPARATUS.

The main purpose of this chapter is to give descriptions of the methods and apparatus used in pharmacologic experimentation on animals. Students who have taken a course in experimental physiology will be familiar with most of these methods; for this reason it seemed preferable to separate their description from that of the experiments proper. Only those methods, which are actually used in the ordinary course, are given in detail; but it is hoped that the references to the others will be sufficient to guide the more advanced worker. It should be remembered that in the matter of technic, a little demonstrating is superior to pages of description.

I. ELECTRIC AND RECORDING APPARATUS.

The Induction Coil.— Figure 95 gives an illustration of a simple and effective form. If the *tetanizing current* is required, the binding screws *a* and *b* are connected with the battery, the primary key *Kp* being closed whenever the current is to be used. For *single make and break shocks*, the battery is connected with *a* and *c*, and make and break are made by pushing down or releasing *Kp*.

i is the interrupter which produces the *tetanizing current* if the battery is connected with *a* and *b*. *p* is the primary coil which surrounds a bundle of soft iron wire. The latter serves at the same time as a magnet for the interrupter. The secondary coil *S* ends in two binding screws *s' s'*, to which the *electrodes* are attached. If these are to be used on the nerve, they are best made from flexible insulated wire to which short pins are soldered, the ends being inclosed in glass tubing and bound together. For direct stimulation of the muscle, however, a better arrangement is to connect *s'* with the muscle by means of very fine insulated wires the bared ends of which are thrust directly through the muscle. Platinum and non-polarizable electrodes are not necessary in the ordinary course.

To produce a *single break shock, s'* is connected with the binding screws of another key, *Ks*. The electrodes (*e, e*) are connected with the same binding post. (See Fig. 95.) When *Ks* is closed, the secondary current is short-circuited. To send a single break shock into the muscle: With the finger close *Ks*, then *Kp*, then open *Ks*. When *Kp* is now opened, a single break shock will be thrown into the muscle.

The rail on which the secondary coil slides should be provided with a centimeter scale to enable one to reproduce the same strength of current.

Always test the coil by placing the electrodes on a muscle, or on the tongue, before beginning the experiment.

If the induction coil does not work *brighten the connections with sand paper*. Test the primary circuit, by placing the wires on the tongue; if this shows a defect, test the battery in the same way. If the trouble is not in the primary circuit, see whether the electrodes are short circuited, by placing the moistened fingers on the binding-screws of the secondary coil.

The Harvard Inductorium.— In this the outer binding posts are used for the *tetanizing current;* the left outer post and the middle post for *single shocks.* The secondary current can be short-circuited by closing the key at the end of the rods. The current is weakened by drawing out the secondary coil and turning it on its axis.

Batteries.— The ordinary dry cells are the most convenient. They suffice for most purposes, although they do not give a very steady current. If the latter is essential, the Daniell cell is the most useful.

Simple Electric Keys.—The form shown in Fig. 95 is easily made, or can be bought. Small electric light switches answer for many purposes.

Single Shock Key.—The apparatus shown in Fig. 96 makes it possible to produce a single break induction shock by one movement.

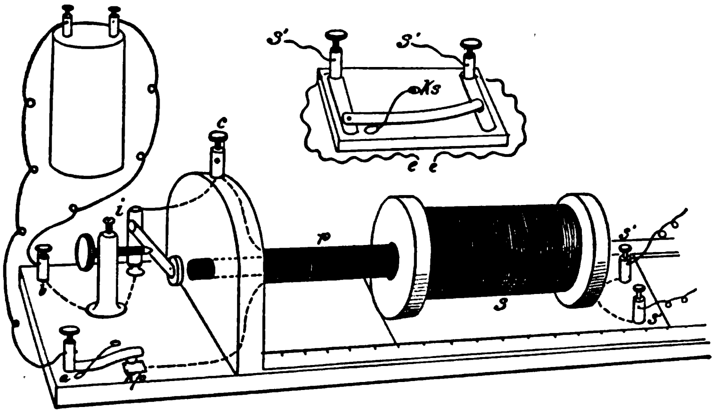

Fig. 95.— Induction coil and simple key. (For description, see the text.)

Kymographs.— These are cylinders which are moved automatically by a clockwork, motor, etc. (see Fig. 111, page 812). Three speeds are needed: one revolution in 5 to 10 seconds (for frog's muscle); in 5 minutes (for details of blood-pressure, etc.); and ½ hour (for prolonged blood-pressure, respiration, etc.). The cylinder is covered with paper, on which the recording instrument writes. The paper is drawn snugly around the drum, the free edge of the paper being pasted with mucilage on to the first layer. Superfluous paper is trimmed off. The writing may be done with ink from a small glass feeding tube attached to the writing instrument. A more generally useful method, however, is to use a paper with glazed surface and covered with a thin layer of soot, on which the levers, etc., trace. The soot is deposited by revolving the drum rapidly in the flame of a fish-tail burner. A stand for supporting the drum whilst it is being revolved and smoked can easily be constructed from a small box. The tracing is always started where the paper joins. When the tracing has been taken, the paper is cut from the drum, and varnished by passing it through a trough containing a strong alcoholic solution of orange shellac. Any notes, etc., must be written with a blunt needle on the tracing before it is varnished. They should be sufficient to make the tracing intelligible without reference to note-books.

Blue prints of tracings may be made by laying the tracing on a sheet of sensitive blue print paper, covering with a plate of glass, and exposing to sunlight for a day, and washing.

For **writing points** one may use tapering bits of parchment paper, 5 cm. long, and 1 cm. wide at the base. These are attached to the end of the straw-levers, etc., by sealing wax or colophonium cement. Points of celluloid or steel, or the blunt end of a needle, can be similarly used. The end of the writing point should be bent slightly toward the drum. It should be placed at a tangent, pointing in the direction toward which the drum is moving.

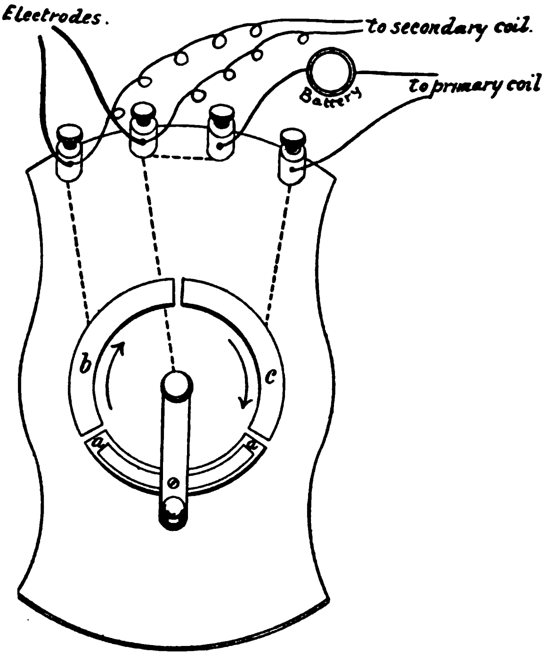

Fig. 96.— Single Shock Key (⅓ natural size). Three segments of brass, a, b, c, are mounted in a circle on a wooden or slade base, being carefully insulated from each other. They are connected with binding screws as shown in the dotted lines. A metal crank is mounted in the center of this circle. This presses on the brass segments by a cross-piece. The binding screws are connected as shown in the diagram. When not in use, the crank is kept at a. To stimulate, it is turned in the direction of the arrow. Stimulation occurs when the crank leaves c for a.

The movements to be recorded are usually so small that they require to be magnified by levers (see Muscle-levers): these should be rigid and light. Straws or aluminium are very satisfactory.

Stands for Supporting Levers, Etc.—A rather short stand with heavy semicircular base is best. It is furnished with double clamps

(" mouffen"). An *adjustable* stand is very convenient if great accuracy of adjustment is needed. This is secured by a micrometer screw.

II. EXPERIMENTS ON FROGS.

" Medium" frogs, of a body-length of 2 to 3 inches, answer very well; the larger specimens should be reserved for perfusion experiments on the heart. The animals should be kept in a roomy tank, with cold running water and a dry shelf or some stones.

Administration of Drugs.— Solutions are usually injected into the anterior lymph-sac. The method of Edmunds and Cushny is recommended: " Lay the animal back downwards in the palm of the left hand. Hold one of its forelegs firmly between the thumb and index finger, and the other foreleg between the middle and ring fingers. Draw its hindlegs downward and hold them against the palmar surface of the hand by means of the little finger.

" Having the drug in the glass injecting pipette, which is held in the right hand, force the animal's mouth open with the point. Pass the pipette into the mouth, avoiding the tongue, which is attached anteriorly, and direct the point toward the floor of the mouth which with a little pressure it will pierce, entering the lymph-sac. As it is pushed down the sac, the point can be seen beneath the skin of the abdominal wall. The finger is now removed, and the drug allowed to flow into the sac, or if necessary, blown in."

When very accurate dosage is desired, an exact pipette, furnished with a hypodermic needle, may be employed. Ordinarily, a pipette graduated by the student with file marks into ¼ c. c., will suffice. The quantity injected should lie between 0.5 and 1 c. c. (see Index, " Calculation of Doses and Dilutions).

Solutions can also be given by the *stomach,* through a blunt glass-tube passed down the esophagus. Many water-soluble drugs (alkaloidal salts, etc.) are absorbed by the *intact skin,* and may be administered by painting them on the surface of the skin, or by placing the entire animal in a jar containing the solution. *Gases* can be given by placing the animal under an inverted tumbler.

Anesthesia may be induced by placing a bunch of cotton saturated with ether under the tumbler.

To pith a frog, it is held in the left hand and the head bent slightly forward with the thumb. If the finger-nail is passed lightly along the spine a slight depression will be felt back of the head. A narrow-bladed knife is thrust in here, and the brain or cord can then be destroyed by pushing in a stiff wire. When this is withdrawn, the wound should be stopped with a short piece of pointed match to avoid bleeding. A special wire (the thickness of a pencil-lead and 4 inches long) should be reserved for this purpose.

The brain and medulla alone are destroyed when the animal is to be used for the observation of reflexes or circulation. The cord also, when the organs (heart or muscle) are to be excised.

To destroy the brain only, a line is drawn joining the posterior edge of the tympanic membranes, and the skull opened in front of this line and the brain destroyed.

Observation of Reflex Time.— The frog (usually with brain and medulla pithed) is held with forceps or suspended from a hook passed through the lower jaw, and one or both hind-feet immersed into a dish containing 5% acetic acid or $^1/_{10}$% HCl. The reflex time is the time elapsing between the immersion and the withdrawal of the foot. The average of several observations should be taken, the acid being washed off after each test, and a short interval of rest must be given.

Frog-boards.— For dissections or operations, the pithed frog should be pinned in convenient position on a cork board. Plates of cork 12 × 4 × $^3/_{16}$ inches can be obtained from dealers in shoemaker's supplies. These are cut to a length of six inches and may be tacked to small pine boards of about the same size.

For observing the circulation of the frog's foot, a triangular slit is cut from one end of the board, and the web of the foot is stretched over this slit. This is laid on the stage of the microscope, the other end of the board being conveniently supported by a tumbler.

For *observing the circulation in the omentum,* the cork-board shown in Fig. 97 is employed. A semicircle is cut out at one side to adapt it to the stand of the microscope. A hole of about 18 mm. is made near the center with a cork-borer. Into this a perforated cork (1 cm. bore) is pushed tightly. The bottom of the cork is cut off flush with the board. The top projects 1 cm. above the board. The edges of the cork are rounded with a file.

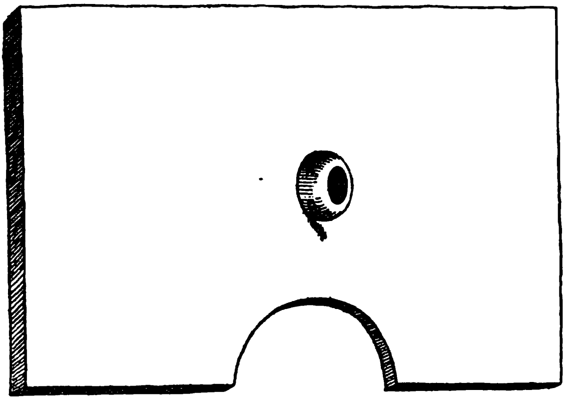

Fig. 97.— Circulation-Board, for studying the circulation in the frog's omentum. ½ natural size.

To observe the circulation, the brain of the frog is pithed. The abdomen is opened and the sciatic nerves divided within the abdomen. The frog is then pinned on the board, on the side away from the microscope, so that the abdomen touches the cork. A small pledget of cotton, moistened with normal saline solution, is inserted between the frog and the cork. A coil of intestine is drawn out carefully, and pinned over the cork, so that the mesentery comes to lie over the opening. Twisting of the vessels must be avoided. A triangular piece of filter paper is laid with its base on the opened abdomen, and its apex on the mesentery. This is moistened with normal saline solution.

Normal Saline Solution for Frogs.— This is a 0.75% solution of sodium chlorid.

Preparation of the Sciatic Nerve.— The frog is pithed and an incision is made through the skin from the hip to the knee, about the middle of the dorsal surface of the leg. By separating the muscles with the forceps, the nerve is seen as a whitish cord at the bottom of the groove. It may be raised by gently passing a thread under it with a frog-needle.[1] Care must be taken not to injure it by handling.

To Ligate the Leg exclusive of the Sciatic Nerve, the nerve is prepared as just described, and a stout linen ligatured is passed below it and tied firmly around the leg, including all the blood-vessels. The nerve must be protected against drying by covering it with filter paper soaked in 0.6% NaCl.

To make a muscle-nerve preparation, the frog is pithed through brain and cord. It is then held up by the legs so that the anterior part of the body falls down. The scissors are thrust through the body a little anterior to the angle and the whole body is cut off.† By grasping the skin with a cloth it can be readily removed from the legs. The two legs are then cut apart just in the median line. The iliac bones (the two bones at the sides) are cut away. Each portion is then turned with the posterior surface upward, and the muscles of the thigh are pulled apart with the fingers. The sciatic nerve will be seen lying at the bottom of the groove. It is carefully dissected out with a few cuts of the scissors, from the spinal canal to which it is attached, to the knee. The thigh is then cut off so as to leave a short piece of the femur attached to the knee.— A blade of the scissors is then thrust under the tendo Achillis, and pushed as far as possible toward the toes. The tendon is then cut off at this point. The tibial bone is also divided close to the knee.— In this way a preparation is formed consisting of a small piece of bone of the spinal column attached to the sciatic nerve, a bit of the femur, the gastrocnemius muscle, and the tendo Achillis. These preparations must be carefully kept from drying by wrapping in filter paper soaked in normal saline solution.

If the drugs are not to be applied directly to the muscle, the skin may be left on the preparation. If the poison is to be applied only to the nerve, the operation need only to be carried to †.

Gastrocnemius Preparations.— If the muscle alone is to be observed, the preparation of the nerve may be dispensed with. The leg is amputated just above the knee. If the muscle is not to be exposed to the poisons, this preparation may be used as it is. Otherwise the skin may be removed and the muscle prepared as in — to — of the last paragraph.

It is sometimes desirable to obtain a record of muscular contractions whilst the circulation through the muscle is intact. For this purpose the pithed frog is pinned on the board, dorsal surface up, and a ligature is passed through the tendo Achillis and attached to the lever.

Protection Against Drying.— The muscle and nerve must be carefully protected from desiccation. This is superfluous if the preparation is covered by skin; otherwise, it may be wrapped in filter paper saturated with normal saline solution. The nerve may be painted with the solution, using a camel's hair brush or swab. If it is necessary to keep the moisture constant, the preparation is covered by a tumbler or bell-jar lined with moist filter paper. A "moist chamber" is made by the Harvard Apparatus Company.

Direct Application of Drugs to the Muscle or Nerve.— This may be done, according to circumstances, by dipping the part into the solution, or by painting with a camel's hair brush, or by allowing the solution to flow over the part from a pipette. The penetration of solutions into the muscle may be facilitated by scarifying the sheath.

Gases may be applied by placing the preparation, or any part of it, into a tube through which the moist gas is flowing (Harvard Gas Chamber).

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[1] *Frog Needles* are made by heating a stout sewing needle half an inch from the blunt end until it can be bent at right angles and fixing the point in a convenient wooden handle (penholder).

Heating and Cooling the Muscle.— The muscle may be heated or cooled by laying it into normal saline solution of the required temperature. Better results can be obtained by surrounding the muscle with a box containing water at the proper temperature (Harvard Muscle Warmer).

Muscle-Levers.— To record the movement of a muscle graphically, to obtain a *muscle-tracing*, it requires to be magnified by a lever. The type illustrated in Fig. 98 is the most useful for pharmacologic purposes, as it permits the application of solutions without removing the lever from the drum.

A straw or light strip of aluminium, about 5 inches long, is tied to the lever and fixed with wax. This again bears a writing point of parchment paper.

The muscle is attached by hooks or strings, as shown in the figure. The attachment to the lever is best made with a bent pin, so that the point of attachment, and thereby the excursion, can be altered as needed. A weight of about 10 Gm. should be suspended on the other limb, about an equal distance from the fulcrum. The nerve may be laid on the electrodes. If the muscle is to be stimulated directly, fine wires, connected with the secondary coil, are thrust directly through the muscle.

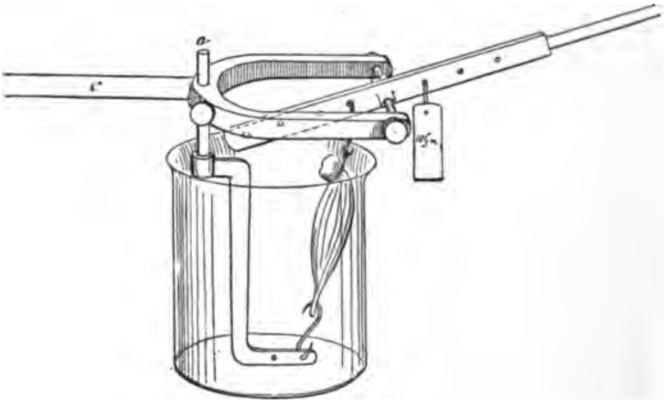

Fig. 98.— Muscle lever, natural size.

Single break shocks (see Index) are used, unless the muscle is to be tetanized. The lever is adjusted at a tangent to the drum, until it traces easily when the lever is moved. The writing point should be bent toward the drum. The fastest speed of the drum is needed *to show the form of contraction*. This may be secured by raising the drum from the clockwork, and spinning it like a top, by a weight attached to a cord which is wound about the drum. The tracing should be taken immediately after the weight has fallen.

If it is wished to stimulate the muscle always at the same point of the drum, the arrangement described in Stewart's Manual may be used.

The effect of a solution is tested by placing it in beaker or test-tube, and raising this so as to immerse the muscle.

A *time record* may be placed on the tracing by a writing-point attached to a vibrating tuning fork.

To study the effect of drugs on fatigue, the two gastrocnemii of the same animal are employed, one being treated with normal saline, the other with the drug dissolved in saline. The two muscles are then tied to levers, which are arranged so as to write on the same (slow) drum. The magnification, load, friction, etc., should be exactly equal. Each muscle is then connected with one of the binding screws of the secondary coil. A third wire joins the two muscles. A tetanizing current is employed. The results are apt to be unsatisfactory unless the experiment is very carefully performed.

The Lifting Power of a Muscle.— A convenient apparatus for studying this consists in a stiff straight brass wire (4 mm. diameter), about 6 inches long. One end of the wire is securely clamped to a stand; the other is prolonged by a straw, to exaggerate the movement. A stiff iron rod (¼ inch diameter, 6 inches long) is clamped on the same stand, 3 inches above and parallel to the brass wire. The muscle is tied to the two rods, so that it may be moved toward or away from the stand. The nearest point to the stand is noted, at which stimulation of the muscle causes a perceptible movement of the lever. This will be the nearer, the greater the lifting power of the muscle.

Another method is as follows: The muscle is connected with a Harvard muscle lever, which is supported by the after-load screw. A weight-pan is suspended from the lever at the point where the muscle is attached, and weights are added until the muscle is just unable to move the lever when stimulated.

The excitability of a muscle or nerve is observed very simply by noticing the greatest distance or angle of the secondary coil, which will just give a contraction (single break shocks). Care must be used that the electrodes make good and equal contact.

To compare the effect of a drug on muscle and nerve, two muscle nerve preparations (page 797) are made from the same animal. A microscopic slide is placed in an evaporating dish, so as to form a bench, and the bottom of the dish is filled with the solution (which should not touch the slide). The two preparations are now arranged so that the nerve of one and the muscle of the other are in the solution, whilst the muscle of the first and the nerve of the second lie on the bench, *i. e.,* outside of the solution.

The **technic of electro-physiology** is given in Stewart's Manual.

Ciliary Movement.— A pithed frog is pinned on a board, abdomen upward. The lower jaw is cut off and the esophagus is opened. The rate of motion is measured by observing the time which a very small bit of cork requires to travel between two pin-pricks. The mucosa must be kept moist by saline solution. The *cilioscribe* (Dixon and Inchley, 1905) allows more accurate study.

To **expose the heart,** the frog is pithed, brain only. An incision is then made in the median line through the abdomen and the upper part of the body. The cartilage between the arms is divided and the arms are pulled well apart and fixed to a small board with pins. The heart can then be seen beating. If it is to be treated with reagents, the pericardium should be opened. The frog's heart will be seen to consist of two auricles and a single ventricle. From the ventricle arises a small, whitish bulbus aortæ, and from this the two aortæ. If the heart is turned up, it will be seen that the auricles are continued into the sinus venosus. A white line marks the junction of the two. The stimulation of this line stimulates the vagus ganglia. If the heart is to be handled considerably, it will be convenient to place a silk ligature around the frenum, the delicate fibrous band attaching the lower surface of the heart to the pericardium. This can then be divided and the heart turned by the ligature. If drugs are to be applied, this is conveniently done with a pipette or a camel's hair pencil.

The vagus trunk comes to the surface at about the angle of the jaw, in company with the glossopharyngeal and hypoglossal nerves, lying between the two. By exposing this area the vagus can easily be seen passing to the heart (Fig. 99). It may be dissected out and placed on a ligature for stimulation, but frequently it suffices to stimulate it *in situ*.

For the dissection of the *accelerator nerve*, see Stewart's Manual.

Cardiac Tracings.— As a general rule, more can be learned by direct inspection of the heart, than by tracings. These may be taken either by (*a*) resting a light lever directly on the heart; or (*b*) by attaching a small piece of cork to the muscle-lever, in place of the weight, and resting this weight on the heart; or (*c*), by the suspension method, passing a fine thread around or through the apex, and connecting with a muscle-lever (Heinz, I, p. 820); or (*d*) by connecting one of the aortæ with a small mercury manometer (see "Blood-pressure"). When levers are used with the heart, they should be light and well balanced.

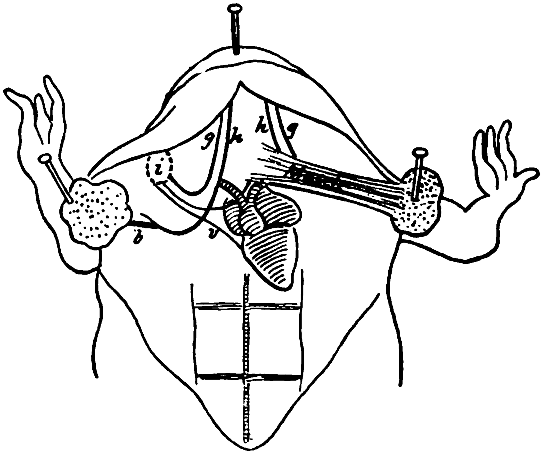

Fig. 99.— Dissection of vagus, frog: *v*. Vagus nerve; *h*, hypoglossal nerve; *g*, glosso-pharyngeal nerve; *b*, brachial plexus; *j*, jaw.

Perfusion of the Frog's Heart.— The most convenient method consists in placing cannulæ (see Index) into the ascending vena cava and in one of the aortæ, both pointing toward the heart, and ligating the other vessels. The vein cannula is connected by rubber tubing with a small funnel or a bulb, shaped as in Fig. 102. Air bubbles must be rigorously excluded. The aortic cannula is also connected with a tube, through which the fluid can return to the reservoir. The latter is filled with the perfusing fluid — Ringer's solution, preferably with the addition of 10 to 25% of defibrinated herbivorous blood. By raising the reservoir, the diastolic pressure can be varied at will — 10 to 20 cm. gives the best results. The resistance to the heart can be varied by raising or partially clamping the aortic tube.

The observations are made by counting the number of beats and the outflow per minute. Tracings may be taken by any of the methods. The heart may be left in the body, or excised.

If drugs are to be perfused, it is well to connect the vein cannula with two reservoirs by a small Y tube, the tubes being furnished with Mohr's clamps. Both reservoirs must be at the same level. Much weaker solutions of drugs are employed in the perfusion than those which are dropped on the surface of the heart.

If it is desired to keep the diastolic pressure perfectly constant, the bulbs (or "aspirator" bottles) are provided with a **Mariotte stopper** — a perforated stopper with a glass tube passing to near the bottom of the tube. The pressure is taken from the lower end of this tube, no matter what the level of the liquid.

For a description of the more complicated **Williams' Apparatus,** see Index.

Experiments on Turtles' Hearts. — These are in some respects superior to those on the frog, the structures being larger and more resistant. The technic is the same. The brain is pithed, and the heart exposed by sawing off the plastron. The animal can be supported on its back in a ring formed with a towel. The vagus accompanies the carotid artery.

Strips of the ventricle may be cut by opening the pericardium, grasping the left angle of the base of the ventricle with forceps, and cutting around the apex to the opposite side. This piece may be cut into 2 or three strips, and attached to the muscle lever, precisely like a gastrocnemius preparation, keeping it immersed in Ringer's Fluid (Greene).

Heart of Chick Embryos.— Eggs are incubated for 24 to 36 hours, carefully opened, the contents floated into a dish, and the membranes cut away. The heart-beat may be observed in a watchglass, under the microscope, and drugs applied, etc. The heart at this time does not contain nerves. (Pickering, 1893.)

Perfusion of the Vessels of the Frog.— The heart of the pithed frog is exposed. One aorta is tied and a cannula is tied in the other aorta, pointing peripherally. This is connected with perfusion reservoirs with Ringer's Fluid. The vinus venosus is cut. The frog is suspended over a graduate, by which the outflow is measured.

Movements of the Stomach.— See Practical Physiology, Beddard, etc.

III. EXPERIMENTS ON MAN.

Numerous actions of drugs can be demonstrated on the student or on patients without special apparatus — the effects on respiration, pulse, pupil, diuresis, taste, local and general anesthesia, psychic effects, etc.

These observations are the more valuable if they are taken in connection with the ward-work, and supplemented by the use of the clinical instruments of observation: thermometer, sphygmomanometer, sphygmograph, etc. Experiments with the plethysmograph, cardiograph, esthesiometer, etc., come under the same heading. The technic is described in Stewart's Manual. Ergographic experiments are also useful. The Harvard spring ergograph suffices for demonstrating the effects of drugs.

IV. EXPERIMENTS ON MAMMALS.

Anesthesia.— *Operations are to be made only under complete surgical anesthesia.* — The method of anesthesia depends to some extent on the animal.

Dogs.—*Morphin-Ether Anesthesia.* — 0.02 Gm. of Morphin per Kg. (hydrochlorid or sulphate, 0.5 c. c. per Kg. of 4% solution) is injected hypodermically (before the laboratory time) and followed in half an hour or an hour by the inhalation of ether (see Exercise 58).

Volatile anesthetics may be given to animals on cotton covered with a towel, taking care to cover the whole mouth of the animal. When long-continued anesthesia is required and the trachea is to be opened in the experiment, the anesthetic is continued through the tracheal cannula. An arrangement as in Fig. 100 is very useful for this purpose. It consists of a Woulf's bottle containing the anesthetic. The tracheal cannula is connected with one mouth of the bottle and prevented from falling in by a screw-cock. The other mouth bears another tube, which can be narrowed by another screw-cock. By adjusting these cocks the amount of anesthetics can be increased or diminished. In the illustration is shown the manner of connecting this with Marey's tambour for taking **respiratory tracings.** The cocks may generally be dispensed with.

Chloroform, or an *A. C. E. mixture* (of equal parts of Alcohol, Chloroform, and Ether) may be substituted for the ether; but they lower the blood-pressure and are more dangerous.

Ethyl Chlorid is useful for very short operations. It may be given without morphin, by spraying it on some cotton placed in the bottom of a tumbler, which is then inverted over the mouth and wrapped with a towel. Better results are secured by giving it in gas-form through a special mask.

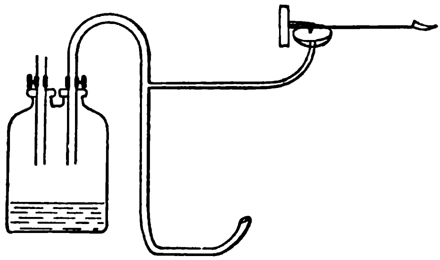

Fig. 100.— Woulf's bottle for giving anesthetic (also arranged for respiratory tracing).

Morphin-Chloretone Anesthesia.— This has the advantage that it requires no attention, the animal remaining completely anesthetized for several hours. It cannot be used if the animal is to recover from the operation. The morphin is injected, as above. After 1 to 3 hours, 0.2 Gm. per Kg. of chloretone, dissolved in a small quantity of alcohol, is injected through a stomach-tube.

Grehant Anesthesia (1905).— This possesses all the advantages of the chloretone method, but is more safe. (It has not been tested sufficiently in survival experiments, but can probably be used.) The animal is given a hypodermic injection of 0.01 gm. per Kg. of morphin (¼ c. c. per Kg. of 4%), followed in half an hour by 10 c. c. per Kg. of the mixture, diluted with water to make a total of 200 c. c., administered by the stomach tube. The anesthesia is complete in 5 to 15 minutes and lasts for 8 to 14 hours. The mixture consists of: chloroform, 50 c. c.; alcohol and water, each 500 c. c.

Cats.— *Ether Anesthesia.*— The animal is placed in a tight box or bell-jar, into which are dropped sponges saturated with ether, until the required degree of anesthesia is procured.

Morphin-Chloretone Anesthesia (Edmunds and Cushny).— The animal is placed in a box, 35 cm. long, 18 cm. wide, and 18 cm. deep. The box is furnished with a sliding lid. A V shaped cut is made in the end of the lid and in the corresponding end of the box, so that the animal may be securely clamped in this opening, allowing the head to protrude. The lid is fixed with a nail. 40 to 60 mg. of morphin are injected with a hypodermic syringe into the skin of the neck. This is followed by 0.3 Gm. per Kg. of chloretone dissolved in alcohol, administered by a stomach-tube.

Rabbits.— One of the following anesthetics may be given by *stomach-*

tube: Urethane, 1 Gm. per Kg., dissolved in water; *Paraldehyd,* 1 Gm. per Kg., undiluted; *Chloral,* 0.6 Gm. per Kg., in water.

An easier and better method consists in injecting the drugs into the *rectum* by a catheter, clamping the anus with a bull-dog forceps after the injection is finished. The doses by this method are: *Urethane,* 0.75 Gm. per Kg., in water; *Paraldehyd,* 1 Gm. per Kg., undiluted; *Chloral,* 0.3 Gm. per Kg., in water.

Morphin (50 mg.), hypodermically, also secures a good anesthesia. About fifteen to twenty minutes are allowed for the development of the narcosis. If this is incomplete, it may be *supplemented by the inhalation of ether.* Chloroform is rather too dangerous for these animals.

The Administration of Anesthetics.— The anesthetizer should bestow as much attention on the animal as if it were a patient. It should be kept warm by covering with a towel or cotton. Complete muscular relaxation is the best index of sufficient anesthesia. The conjunctival reflex may remain. The attention should be fixed mainly on the respiration. If this stops, artificial respiration should be started without delay. If unsuccessful, other methods should be tried (see Exercise 58). With morphinized animals, very little of the anesthetic suffices, after the operating is completed. The anesthetic should be completely withdrawn whenever an injection is made.

The anesthesia may be kept approximately equal by dropping it at a uniform rate; but if this point is essential, it is better to employ the Gréhant method.

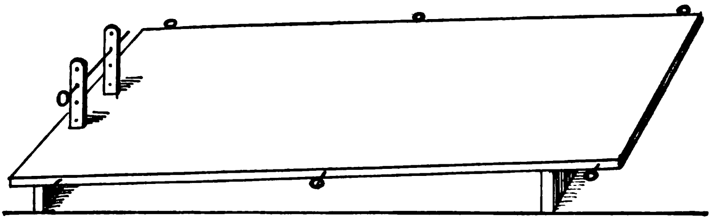

Fig. 101.— Dog board.

Holding the Animals.— In administering drugs without anesthesia, the animal should be held securely between the knees of an assistant.

Animal Boards.— For convenience in operating, the anesthetized animals should be tied to a board. A number of complicated holders are in use, but the one illustrated in Fig. 101 is cheap and answers almost every purpose.

A number of sizes should be on hand for different sized animals (1 × 4 feet for dogs; 8 × 30 inches for rabbits). The crosspiece is made of wire, $^3/_{16}$ inch in diameter. It is pushed back of the canine teeth. A 2-foot piece of stout twine[1] is passed under the neck, behind the ears, the ends are brought forward, wound tightly around the wire, and tied about the mouth. This holds the head very securely. In operating on the neck the front legs should be tied toward the abdomen; in operating on the chest, they are secured toward the head.

The Administration of Drugs.— To *give a drug by stomach,* a stout, soft gum catheter (No. 10, English scale) is attached to a feeding bulb.[2] (Fig. 102).

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[1] India hemp No. 3 for dogs; dauntless flax No. 24 for rabbits.

[2] These are not on the market and have to be made to order.

The mouth of the animal is held open with a notched stick, the head of the animal is bent forward, and the moistened catheter is passed well back, when no difficulty will be found in making it enter the esophagus. Care must be taken not to push it into the trachea, and it is well to note that the animal does not breathe through the catheter. The accident may also be discovered by the fact that the catheter can not be pushed as far and that the fluid flows in with much greater difficulty. The solution is then poured into the bulb. If it does not flow readily, it can be quickened by blowing.

Measuring Solutions.— Small quantities should be measured with a pipette. The syringe, etc., should be rinsed with a little water and this should also be injected, to insure that the animal receives the full calculated quantity.

The administration per rectum is done with the same form of apparatus as is used in the stomach. The catheter should be introduced as high as possible. The anus is then closed with bulldog forceps.

Hypodermic injections are generally made under the loose skin of the flank — the animal being held securely. The volume of fluid should be kept below 1 c. c. for guinea pigs, and below 5 c. c. for dogs (see Calculation of Doses and Dilutions, below). If it is necessary to inject larger quantities, they should be given in fractions, distributed over several parts of the body. The injection of irritant substances should be avoided.

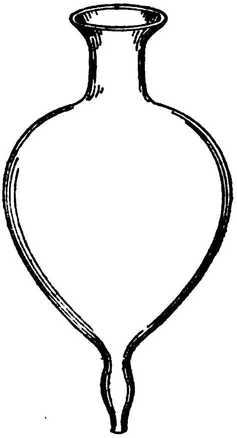

Fig. 102.— Feeding Bulb (made of a capacity of 100 c. c.).

An ordinary (1 c. c.) *hypodermic syringe* and strong "antitoxin" needle answers for the smaller quantities; a 5 c. c. antitoxin syringe with an "aspirator" needle is used for dogs.

Intramuscular injections are generally made into the gluteal muscles. *Intraperitoneal and intrapleural injections* are made by thrusting in the small needle, perpendicular to the surface of the body.

For **intravenous injections,** a cannula is tied into a vein, pointing toward the heart, and this is connected with a burette containing the solution. The rubber connection should be short, to avoid dead space. It is closed by a Mohr's clamp. If the injection is to be made slowly, a screw-clamp must be placed on the rubber tube. The greatest care must be used to avoid the entrance of air bubbles into the vein. Before connecting, the rubber tube should be completely filled with the solution, and the cannula should also be filled (with a pipette). If the volume of the injected fluid is small, it may be introduced at air temperature; if it exceeds 10 c. c., it should be brought to body temperature. (Greene advises to surround the burette with the jacket of a Liebig's condenser, through which water of the desired temperature is circulated.)

If a number of small injections of different drugs are to be made in quick succession, it may be more convenient to clamp the rubber tube a half inch above the cannula, and to make the injection with a hypodermic syringe, thrusting the needle obliquely through the rubber into the cannula.

The injections may be made either into the femoral or jugular vein. The former is preferred, as the jugular injection introduced complications by bringing the drug directly into the heart in too concentrated a form. It may be necessary in small animals, in which it is difficult to introduce a cannula into the femoral vein.

In unanesthetized rabbits, intravenous injections may be made by thrusting the needle of the hypodermic syringe into one of the ear-veins, which has been previously distended by pressure.

Injections into arteries require some pressure. This may be obtained by connecting the top of the syringe with a pressure bottle; or more conveniently, with the compressed-oxygen tank.

The Calculation of Doses and Dilutions.— Remember that one c. c. of a 1 : 1,000 ($^{1}/_{10}\%$) solution contains 1 mg. of drug; of a 1% solution, 10 mg., etc.

Multiply the dose in milligrams by the weight of the animal in kilograms. This gives the absolute dose of the drug. To find the most convenient percentage of solution, divide the milligrams of absolute dose by the number of c. c. of solution which you wish to use and multiply the product by 0.1. This gives the percentage. For instance, you wish to inject 90 mg., in such dilution that from 1 to 5 c. c. will be needed. 1 c. c. would require a $^{90}/_{1} \times 0.1 =$ a 9% solution; 5 c. c. would require $^{90}/_{5} \times 0.1 =$ a 1.8% solution. Anything between these limits will answer. Say that a 5% solution is at hand. Each c. c. of this would equal 50 mg. You wish 90 mg., therefore $^{90}/_{50} = 1.8$ c. c. With a little practice, one soon comes to judge the proper dilutions without the necessity of this calculation.

Work out the following problems and see whether the answers are correct: The dog weighs 8 Kg. You wish to inject 5 to 10 c. c. of each solution. The dose of (*a*) = 0.1 Gm. × Kg.; (*b*) = 5 mg. × Kg.; (*c*) = 0.006 mg. × Kg. What percentage and how much of each solution should be used? Answers: (*a*) 8 c. c. of 10% or 1 : 10; (*b*) 8 c. c. of 0.5% or 1 : 200; (*c*) 4.8 c. c. of 0.001%, or 1 : 100,000.

Cannulae.— A plentiful assortment of different sizes and forms should be on hand. They are best made from glass-tubing. The edges should not be sharp; they may be rounded in the flame, or on a sandstone.

Vessel Cannulæ.— Fig. 103, *a* to *d*, shows the shape and the most useful sizes. *a* is for use in the frog's heart; *b* for rabbit's carotid or dog's femoral artery; *c* for dog's carotid artery or femoral vein; *d* for dog's external jugular. A still smaller size is needed for glandular ducts.

These cannulæ are made by heating the proper size of tubing in a large blow-pipe flame, and drawing it out in the form of Fig. 104. This is allowed to cool, and cut at *a*. The pieces are then heated with a very small pointed flame at ↑, so as to make the shoulder. The ends are cut off as obliquely as possible, by scratching with a triangular file, ground to the proper form on a grindstone, and rounded in the flame. A good cannula should have the end sufficiently large so that it will not slip when tied into the vessels, but no larger.

(In heating glass, it should be constantly rotated in the flame; it is well to push it together *very* gently whilst heating. It should always be removed from the flame before drawing.)

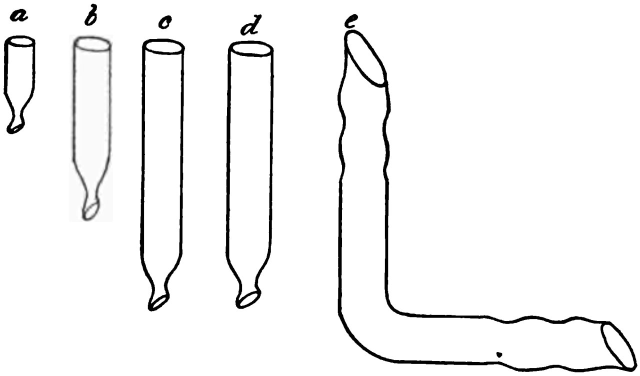

Fig. 103.— Cannulæ for vessels and trachea.

Trachael Cannulæ.— These are of the form shown in Fig. 103 *e*. One end is best made somewhat smaller than the other, so that the same cannula may serve for somewhat different sizes of trachae. Tubing 5 and 8 (Fig. 105) is most useful for rabbits; 9, 10, and 12 for dogs.

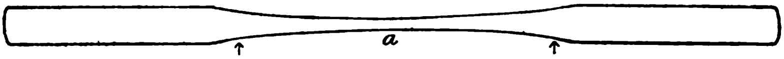

Fig. 104.— Tube drawn for cannulæ or pipettes.

Aortic and Bladder Cannula.— This is made of the form and size of Fig. 106. The rings are made by heating a narrow zone of the tube in a small flame, and pushing the glass together. When used on the bladder, this cannula is tied in the neck. Another bladder cannula, used especially in rabbits, consists of a short thistle tube (Fig. 107). The bladder is cut open and tied as a drum-membrane over the mouth of the cannulæ, the ureters being left free and opening into the cannula.

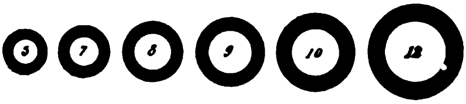

Fig. 105.— Sizes of glass tubing.

Ureter cannulæ are given the form shown in Fig. 108. This is the proper size for dogs. A smaller tube is required for rabbits. The narrow tubing is obtained by using the portion between the arrows in Fig. 104, making this somewhat longer.

Insertion of Cannulæ into Vessels.— The vessel is exposed and cleared of all fascia for the space of an inch, if possible. A bulldog forceps[1] (Fig. 109) is then applied to the end of the vessel toward which the cannula will point. A ligature is passed by forceps or aneurism needle around the vessel near the clamp, and tied into a loose slip-knot. The vessel is then allowed to fill with blood, and another ligature tied securely as far away from the clamp as possible. The vessel is now lifted by the end of the second ligature, and laid on the left index finger. An incision is made with small, curved scissors, near the distal ligature, about two-thirds through the vessel, the moistened point of the cannula is pushed in, and the loose ligature is tied securely around the neck. The ends of the ligatures are now cut off. The largest cannula should be chosen which will fit the vessel without force. The cannula is turned within the vessel so that kinking will not close the opening of the cannula.

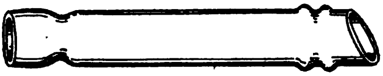
Fig. 106.— Aortic and bladder cannula. Natural size.

The whole procedure is quite easy when the vessels are strong. Delicate vessels should be well distended, and all twisting must be avoided. It may be necessary to hold the vessel open with very fine-pointed forceps. The manipulations must be made very delicately.

Ligatures.— It is a mistake to use ligatures which are too thick. The following are useful sizes: No. 50 linen thread or buttonhole-twist silk for vessels: cotton wrapping twine for trachea, bladder, etc. They should be cut to a length of about six inches. (This may be done in mass by winding the string around the palm of the hand.)

A ligature should be tied as securely as its strength will allow. A little practice will show its limitations. More force can be exerted if the pull is made very near to the knot. A plain double knot is best for small vessels; the bulky surgeon's knot should be confined to larger structures, such as the trachea or aorta.

Ureter cannulæ are introduced in the same manner as described for the vessels; except that the ureter need not be clamped.

The same general method is also used for **inserting the tracheal cannula.** This is exposed, cleaned, two ligatures are placed an inch or two apart, and three or four rings of cartilage are divided with the knife, by a straight or V shaped incision.

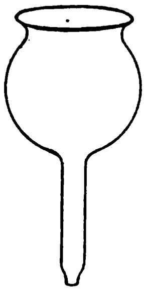
Fig. 107.—Bladder cannula.

Operative Dissections.— The hair of the animal should be well clipped over the field of operation. Scissors (6-inch), curved on the flat, are efficient. The smaller cut hairs are removed by a wet sponge. The wound should be kept as free from blood as possible. This frequently determines the success or failure of a delicate operation. Incisions should be made, if possible, in the median line; the muscles and fasciæ should be separated by blunt dissection. Bleeding vessels are secured by hemostats, and tied. Blood is removed by sponging with small pieces of absorbent cotton. Packing with cotton (or with Pengawahr Djambi) will stop capillary or venous oozing. Practically no blood should be lost in operating on the neck, groin, or abdomen. The wound may be spread by tenaculi, etc., or by weights attached with a cord to hooks.

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[1] When buying these clamps one should take care that the jaws touch along their entire surface.

Operations on the Neck.— The forelegs are tied toward the tail. The structures are most conveniently reached by a median incision, from the lower end of the larynx to near the sternum. The tissues should be divided by layers, keeping to the median line, until the **trachea** is reached. This may be lifted with the fingers and cleaned with the forceps. Tracheotomy is the first step in most pharmacologic experiments, as it facilitates anesthesia and artificial respiration. By feeling outward from the trachea, at the bottom of the wound, the **carotid artery** may be felt pulsating. It is lifted to the surface with the fingers, or by turning the edge of the wound outward. The **vagus nerve** in the dog lies in the same sheath as the artery, and must be carefully and gently separated from it. It should never be included in the arterial ligature. In the *dog,* the vagus trunk includes the **sympathetic and depressor fibers.** These run separately in the *rabbit,* but all in the immediate neighborhood of the artery; they may be recognized by their size, the vagus being the largest, the depressor the smallest. (Illustration in Heinz, I, p. 730.)

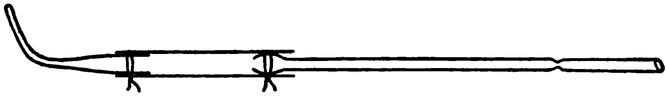

Fig. 108.— Ureter cannula. Natural size.

Stimulation and Division of Nerves.— Nerves must always be manipulated gently. If it is desired to stimulate or divide the vagus, or any other nerve, later in the experiment, a ligature may be passed under it and the ends knotted. The nerve can thus be easily found and lifted from the wound. In other cases, it may be desirable to divide the nerve, securing each end with a ligature. Nerves should always be protected from drying, leaving them in the wound, if possible. In electric stimulation, good contact of the electrodes should be secured. Stimulation of adjacent structures may be prevented by slipping a strip of rubber-dam under the electrodes, or by the use of "shielded" electrodes.

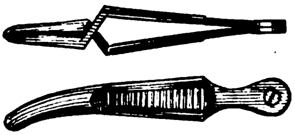

Fig. 109.— Bull dog clamps.

For the dissection of the *Accelerator Nerves,* see Practical Physiology, Beddard, etc.; or Heinz, I, p. 726. A preliminary dissection is indispensable.

The external jugular vein is exposed by blunt dissection between the skin and muscle. It offers no difficulty. It may also be reached directly by a skin incision made about the middle of the neck, in a line drawn from the angle of the jaw to the manubrium.

The **thoracic duct** may also be isolated in the base of the neck. It terminates in the left subclavian vein. A practice-dissection is necessary.

Opening the Thorax.— The animal is deeply morphinized. The forelegs are tied toward the tail. The trachea is connected for artificial respiration. A horseshoe shaped incision is made, through the skin and muscles, from the lower ribs on each side, to and across the manubrium of the sternum. The incision may follow the junction of the cartilage and bone of the ribs. The skin is not stripped off. Artificial respiration is started. The cartilages are now quickly divided and the sternum cut. The plastron is turned down and the bleeding mammary arteries are secured with hemostats. The hemorrhage from the intercostal arteries is insignificant, but may be checked by ligatures. The everted plastron may be sewn to the abdomen. There is usually a very severe fall of blood-pressure. Anesthesia can be kept up by blowing the air through a Woulf's bottle containing ether, or by Gréhant's method. A large sponge soaked in warm water should be kept over the opening, between observations.

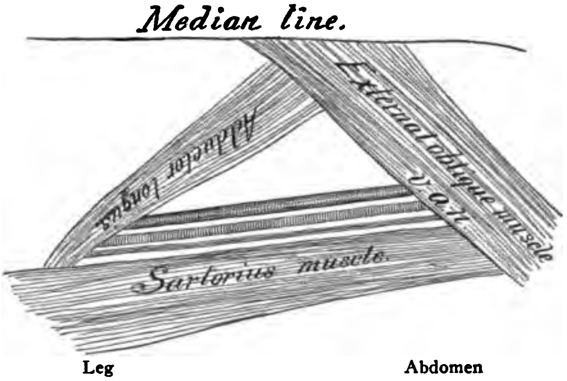

Fig. 110.— Diagram of dissection of femoral vessels, dog. (Brown.)

Exposing the Femoral Vessels.— These may be felt pulsating just below Poupart's ligament, on the outer edge of the stiff adductor longus muscle. The artery lies partly behind and external to the vein (Fig. 110). The cannulæ should be introduced as high as possible. As the vessels give off branches in this region, the dissection must be made carefully.

The **Sciatic Nerve.**— To expose this, the hind leg is held up, and an incision is made through the skin in the median ridge of the posterior surface of the thigh. The muscles are separated with the fingers, keeping a little outward from the middle line. The nerve is felt at the bottom of the wound as a hard cord. The animal should be in deep anesthesia when the nerve is handled.

Opening the Abdomen.— To avoid shock, the exposure of the abdominal organs should be limited as much as possible, both as to area and time. The organs should be kept warm by packing with cotton, and a can filled with hot water should be kept near the animals. In long operations on rabbits, it may be necessary to immerse the whole animal in a warm bath of 0.9% salt solution.

The abdominal incision is made by preference along the linea alba,

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manipul **ation of the Spinal Cord to Exclude the Vasomotor Center.**—
or any eeply anesthetized and tracheotomized dog is laid on the *abdo-*
passed without tying. The neck is rendered prominent by drawing the
found over a sandbag, block, or brick. An incision is made through
skin and muscles, to the spine, from the occiput for a distance of
or four inches. Artificial respiration is started. The cord is
ded between the third and fourth cervical vertebræ. This may be
ne without removing the vertebræ, by pushing a narrow-bladed knife
tween the articulations. It is more certain, however, to expose the
cord. This should be done as quickly as possible, *and the profuse* hemorrhage controlled by packing tightly with small pledgets of cotton. The vasomotor centers may be excluded with absolute certainty by destroying the cord, passing a strong brass rod down *the spinal canal* The extent of the section or destruction must always be controlled by sciatic stimulation and by subsequent autopsy.

If it is desired to paralyze the vasomotor center, the *spine may* be opened from the third cervical vertebra upward. and packed with cotton saturated with 5% cocain solution. This may again be rinsed off after a time.

The technic of operations on the motor areas of the brain is described in Stewart's Manual. The establishment of *permanent fistulæ* which is scarcely suitable for ordinary students' work in pharmacology. is also described in this work. *Aseptic Operations* involve the customary surgical technic.

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Tracings.— The technic of these should be thor-
d, as they constitute one of the most frequent pharma-
ments. They are generally taken from the carotid ar-
are the most suitable subjects. The general arrangement
in Fig. 111.

aratus for Blood-Pressure Tracings.— Mercury Manometer.
g. 112.—This consists of a glass tube, bent as shown in the
ure. No. 9 tubing is used for dogs, No. 7 for rabbits. The straight
imb is about 10 inches high. The tube is mounted on a small board. A cleat may be screwed to the back of this board, about its middle, projecting an inch on one side. This is clamped to the table. It should be leveled so that the vertical tube is plumb. The board also bears a millimeter scale, with arbitrary zero point. The manometer is filled about one-half with mercury. The bent limb is filled with 25% magnesium sulphate solution, and connected with a stiff rubber tube long enough to reach to the carotid cannula. This tube is closed with a pinch-cock (or a lead-tube and metal stop-cock may be substituted, but with little advantage). The connecting tube is also filled with magnesium solution, by means of a long-pointed pipette. The pressure in the manometer is now raised to about the blood-pressure of the animal (say 120 mm.). This may be accomplished simply by forcibly blowing into the rubber tube, clamping near the manometer, and again filling the tube, or, the tube may be connected by a T piece with a perfusion bottle filled with a magnesium solution and raised to the desired level.

For recording the excursions of the manometer, the straight limb bears a float, *f*. This consists of a little cylinder of hard rubber, of the shape and size shown in the figure. It should fit snugly but rather loosely in the tube. It bears a knitting needle, well centered. This again passes through a hard rubber cap, *c*. At the upper extremity this needle carries a small flat piece of cork, to which the writing style is attached. This may be of parchment paper, celluloid, a needle, or a quill pen. The writing point should be bent toward the drum. A few drops of engine oil should be placed in the tube of the manometer. The mercury must not mount above the float. The writing point is held against the drum by a *guide*, consisting of a silk thread, suspended from a wire, and loaded with a 10-gram weight.

The **mean-blood pressure** equals the difference between the read-toward the symphysis pubis. This permits the exposure of loops of *intestine*, of the *spleen*, of the *bladder and uterus*, and of the *ureters* where they end in the bladder.

The *ureters* may be seen posteriorly by lifting out the bladder. (Not to be confused with the spermatic cord!)

(In male animals the incision through the skin is carried just to one side of the penis, the superficial veins are ligated and divided, and the dissection is carried along the fascia until the linea alba is reached.)

To **expose the kidneys**, from the median incision, it is necessary to carry this to near the sternum and to make a second, transverse incision along the lower border of the ribs. They may also be reached from the back, by an incision made about two inches from the spine, from the lower border of the rib obliquely downward. If the incision is made to follow the direction of the muscle, there need be very little bleeding. The spleen and intestine may be reached through the same incision..

The **splanchnic nerves** may be stimulated by placing the electrodes, spread fairly wide apart, about the hilus of the suprarenal gland. This may be reached by the same incision as the kidney. To limit the stimulation strictly to the splanchnics, or to divide these nerves, practice dissections are indispensable. In the rabbit, the splanchnic trunks may be found in the thorax, about the tenth dorsal vertebra, on each side of the aorta. The left is the more easily found in the abdomen. It accompanies the aorta until it terminates in the lower celiac ganglion, just above the left suprarenal gland, on the front of the aorta. The right splanchnic is separated from the aorta, in the abdomen, by the vena cava. It terminates in the superior celiac ganglion, at the level of the right suprarenal gland, in front of the vein.

Destruction of Nerves.— To complete the destruction of nerves, when these accompany vessels, the sheath is painted with concentrated phenol (Bayliss, 1902).

Operations on the Chorda Tympani and Submaxillary Gland.— See Stewart's Manual, or Practical Physiology, Beddard, etc.

Section of the Spinal Cord to Exclude the Vasomotor Center.— The deeply anesthetized and tracheotomized dog is laid on the abdomen, without tying. The neck is rendered prominent by drawing the head over a sandbag, block, or brick. An incision is made through the skin and muscles, to the spine, from the occiput for a distance of three or four inches. Artificial respiration is started. The cord is divided between the third and fourth cervical vertebræ. This may be done without removing the vertebræ, by pushing a narrow-bladed knife between the articulations. It is more certain, however, to expose the cord. This should be done as quickly as possible, and the profuse hemorrhage controlled by packing tightly with small pledgets of cotton. The vasomotor centers may be excluded with absolute certainty by destroying the cord, passing a strong brass rod down the spinal canal.

The extent of the section or destruction must always be controlled by sciatic stimulation and by subsequent autopsy.

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The technic of operations on the motor areas of the brain is described in Stewart's Manual. The establishment of *permanent fistulæ*, which is scarcely suitable for ordinary students' work in pharmacology, is also described in this work. *Aseptic Operations* involve the customary surgical technic.

To **reduce an animal to surgical shock,** it must be completely anesthetized. The intestines are then exposed and manipulated severely.

It is sometimes necessary **to render the blood of an animal noncoagulable;** for instance, in measuring the outflow from veins, or for practicing transfusion.

The best method consists in the intravenous injection of *leech extract.* For each kilo of body-weight, the heads of three leeches are rubbed with sand and 6 c. c. of 0.9% salt solution. This causes apparently no change in the circulation.

The same object may be accomplished by the **Lewaschew-Pick method of defibrination.** About 20 c. c. of blood per kilogram of animal are drawn from an artery, into a porcelain capsule, defibrinated by beating with a glass rod, strained, warmed, and reinjected into a vein. This is repeated every half hour until the blood yields no coagulum. Six or seven defibrinations are needed for this end. *Peptone* is less certain, and causes a considerable fall of blood-pressure. 0.3 to 0.6 Gm. of Witte's peptone per Kilo are injected intravenously (as 5% solution).

The methods of rendering the blood noncoagulable outside of the body will be discussed under Blood-pressure.

Blood-Pressure Tracings.— The technic of these should be thoroughly mastered, as they constitute one of the most frequent pharmacologic experiments. They are generally taken from the carotid artery. Dogs are the most suitable subjects. The general arrangement is shown in Fig. 111.

Apparatus for Blood-Pressure Tracings.— Mercury Manometer. — Fig. 112.— This consists of a glass tube, bent as shown in the figure. No. 9 tubing is used for dogs, No. 7 for rabbits. The straight limb is about 10 inches high. The tube is mounted on a small board. A cleat may be screwed to the back of this board, about its middle, projecting an inch on one side. This is clamped to the table. It should be leveled so that the vertical tube is plumb. The board also bears a millimeter scale, with arbitrary zero point. The manometer is filled about one-half with mercury. The bent limb is filled with 25% magnesium sulphate solution, and connected with a stiff rubber tube long enough to reach to the carotid cannula. This tube is closed with a pinch-cock (or a lead-tube and metal stop-cock may be substituted, but with little advantage). The connecting tube is also filled with magnesium solution, by means of a long-pointed pipette. The pressure in the manometer is now raised to about the blood-pressure of the animal (say 120 mm.). This may be accomplished simply by forcibly blowing into the rubber tube, clamping near the manometer, and again filling the tube, or, the tube may be connected by a T piece with a perfusion bottle filled with a magnesium solution and raised to the desired level.

For recording the excursions of the manometer, the straight limb bears a float, *f.* This consists of a little cylinder of hard rubber, of the shape and size shown in the figure. It should fit snugly but rather loosely in the tube. It bears a knitting needle, well centered. This again passes through a hard rubber cap, *c.* At the upper extremity this needle carries a small flat piece of cork, to which the writing style is attached. This may be of parchment paper, celluloid, a needle, or a quill pen. The writing point should be bent toward the drum. A few drops of engine oil should be placed in the tube of the manometer. The mercury must not mount above the float. The writing point is held against the drum by a *guide,* consisting of a silk thread, suspended from a wire, and loaded with a 10-gram weight.

The **mean-blood pressure** equals the difference between the readings taken at the highest point reached by the mercury in each limb of the manometer. It may also be obtained from the tracing by doubling the distance between the line of zero pressure and the tracing.

This figure for the mean-pressure is only correct if the excursions are small or if the systolic and diastolic variations are of equal duration. If they are not, the excursions may be reduced by a screw clamp on the rubber tube; or the mean-pressure can be calculated from the tracing. A series of vertical lines are drawn from the abscissa to the tracing, at equal intervals. The mean length of these equals one-half the mean-pressure. This calculation is scarcely necessary in most cases — a little judgment will enable one to draw the line of mean-pressure approximately without their aid.

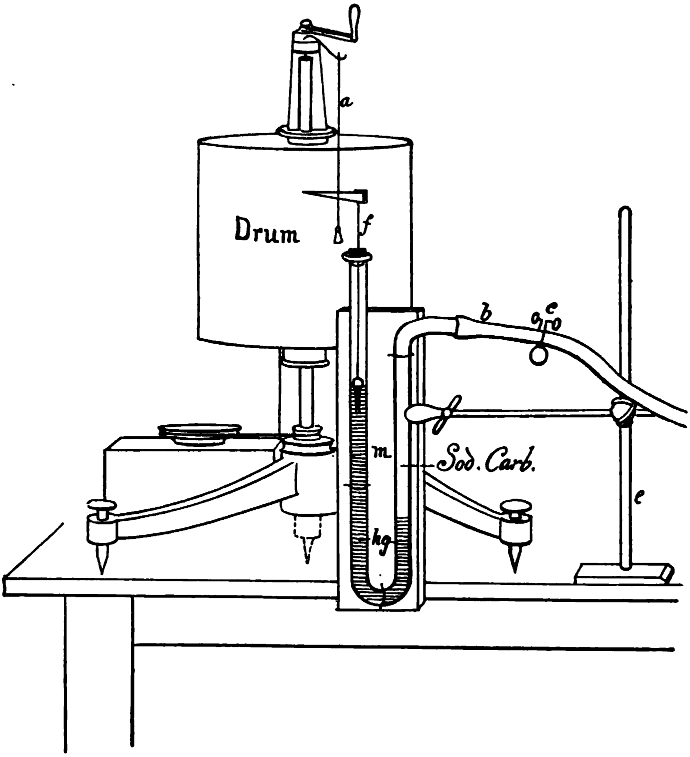

Fig. 111.— Arrangement for taking a blood-pressure tracing (Stewart): *m*, Manometer; *hg*, mercury; *f*, float armed with writing point; *a*, thread attached to a wire projecting from the drum and supporting a small weight; the thread keeps the writing-point in contact with the smoked paper on the drum; *b* is a strong rubber tube connecting the manometer with the artery; *c*, a pinch-cock on the rubber tube, which is taken off when a tracing is to be obtained.

The excursions of the manometer with each heartbeat correspond to the **pulse-pressure.** (The excursions of one limb, as seen on the tracing, must be multiplied by 2.)[1]

The mercury manometer gives only a rough indication of this, the results being vitiated by the inertia of the mercury. It also gives a

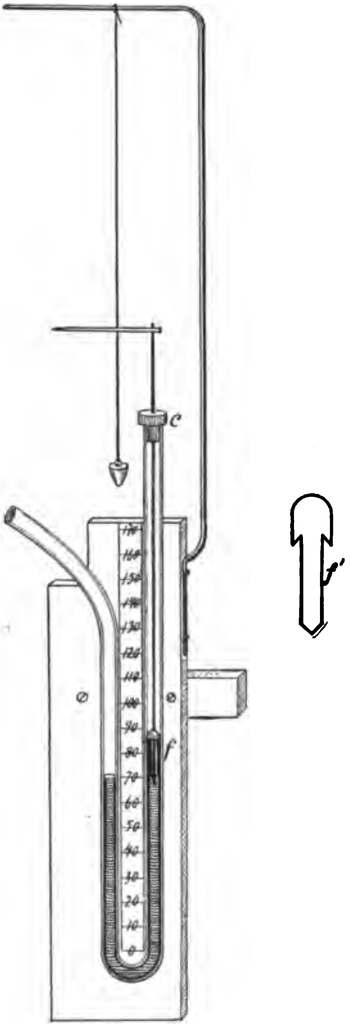

Fig. 112.—Mercury manometer. ¼ natural size; f′, section of float, natural size (Brown).

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[1] Since the tracing represents the excursions in but one limb of the manometer. The mercury in the other limb is of course changed by the same amount. The pressure corresponds to the difference between the two limbs, *i. e.*, to twice that in one limb.

very imperfect picture of the details of the individual pulse waves. An *elastic manometer* (*e. g.*, Huerthle's) is necessary for their accurate study. (See Brodie, Essentials of Practical Physiology.) The mercury manometer is especially useful on account of its simplicity, and for obtaining the mean-pressure. Very good results are obtained by taking simultaneous tracings with both manometers, connecting the mercury with the carotid, and Huerthle's with the femoral.

Signal Magnet.— This is useful for marking the time of injections, stimulations, etc. The Harvard instrument is efficient. The electromagnet is connected with a battery (which may be placed under the table), with the interposition of a key, which is closed. whenever a mark is to be made on the drum. It may be kept closed during the duration of the injection. The writing point of the signal must be exactly on a vertical line with the writing point of the manometer.

The signal may be used to mark the **line of zero-pressure** on the tracing, by adjusting it at the level of the writing point of the manometer when the latter is at zero-pressure (*i. e.*, with the curved limb and rubber tube filled with magnesium sulphate, the rubber tube unclamped, and with its opening dipping into a beaker of the solution, held about the level of the carotid artery of the animal).

It is often useful to draw a straight horizontal line through the tracing at the level of the normal mean-pressure. This may be done, after finishing the tracing, by revolving the drum against a writing point, mounted on a glass rod, adjusted at the proper level.

A *time tracing* may also be added by connecting another signal magnet electrically with a metronome or clock.

Technic of Blood-pressure Tracing.— Smoke the drums. (It is well to always keep an extra smoked cylinder in reserve. The Harvard cylinders are interchangeable.) Set up the manometer and signal and see that they are in good working order. Adjust the signal at zero-pressure. Raise the pressure in the manometer. Adjust the manometer to the drum (where the paper is joined). Adjust the drum so that the manometer writes about the middle. Adjust the guide so that the float will write easily. Adjust the signals on a vertical line with the manometer point. In the meantime, the dog may be prepared, weighed, anesthetized (page 801), tracheotomized if desired (page 807), and a cannula inserted into the (carotid) artery (page 808). Connect the artery with the manometer, avoiding air bubbles. Remove the clamps, and the tracing may be taken. When the tracing is completed, mark the mean normal pressure line, cut the paper from the drum, write the necessary explanations (sufficient to make the tracing intelligible without referring to other notes). Varnish.

A normal tracing should always be taken before the drug is injected. Tracings should also be taken during the injection and whenever any interesting phenomenon occurs. It may be advisable to stop the drum between these periods, especially if a fast speed is used This is not often necessary in using the slow gear and the 10 × 2.2 cm. vane of the Harvard Kymograph, the most generally useful for pharmacologic work. Only a single round of tracings should be taken on each paper. (It is sometimes desirable to take both a slow and a fast tracing at the same time, joining two manometers to the same carotid by a T piece and using two kymographs; this is especially instructive with digitalis and aconite. The slow tracing is made continuous, whilst the fast tracing is only taken at intervals.)

If clotting occurs (*i. e.*, if the manometer ceases to pulsate, whilst the heart can still be felt), the artery and the manometer tube are clamped and disconnected. The cannula is carefully cleaned with a feather, trimmed so as to leave a small plume at the end. The cannula and the end of the rubber tube are filled with magnesium solution, and again connected.

Accidents from the Magnesium Solution.—The 25% (or half-saturated) magnesium sulphate solution has proven the most satisfactory in our hands for the prevention of clotting. Care must be taken, however, that it does not enter the heart, for it causes prompt paralysis of this organ. The danger of this accident is not great, unless too high a preliminary pressure has been produced in the manometer. The effects pass off very quickly, unless the heart is stopped completely. Should this occur, it is often possible to resuscitate the animal by artificial respiration, injection of normal salt solution, and cardiac massage. (Magnesium sulphate must never be used to fill the connection with the injection burrette.)

Other Solutions Used to Prevent Clotting.—Half-saturated sodium sulphate, or 1% sodium citrate, are not as dangerous, but they are also less efficient. Half-saturated sodium carbonate is even more dangerous, and is not advised.

Stephen Hale's Arrangement.—This makes a beautiful demonstration. Instead of using a mercury manometer, the carotid artery is connected with a tube 8 to 12 feet high, formed of long sections of No. 9 glass tubing, joined closely with rubber, and containing a small quantity of oil or leech extract.

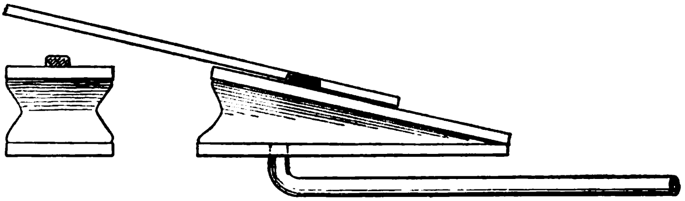

Fig. 113.—Organ-key bellows recorder. Natural size.

Respiratory Tracings.—These are best taken on a separate drum, moving at the same speed as that used for recording the blood-pressure. The levers, etc., are adjusted so that the excursion of the normal respiration has a height of ¼ to 1 inch on the drum. The tracing should be marked to show whether inspiration corresponds to the upstroke or downstroke. Several methods will be described; none is perfectly satisfactory. The tracheal methods *a* and *b* have the advantage that they are not disturbed by movements of the animal. The simple trachea-tambour method (*a*) is the simplest, and suffices if it is desired to obtain a record merely of the rate and depth of the respiration; but it is highly inaccurate when the respiratory excursions are slow or prolonged. This inaccuracy is largely avoided in the bottle-method (*b*); but it introduces the possibility of asphyxiation as a complicating factor. All the other methods are disturbed by movements of the animal. The double tambour (stethograph) method (*c*) suffers less from this, and is perhaps the most generally useful. It can also be used in nonanesthetized animals, if they can be kept sufficiently quiet. This last is also essential for all the lever methods.

Recording Tambours.—The cheapest form consists of a home-made organ-key bellows (Fig. 113), the sides of very thin leather or gold-beater's skin. A 3 or 4 cm. Marey's tambour answers well. The 3 cm. Brodie bellows (made by C. F. Palmer, 6 Upper Tulso Hill, London, N. W.) is the most delicate. All bear a straw and writing point about six inches long.

(a) Simple Trachea-Tambour Method.— Fig. 114. The tracheal cannula is connected with wide tubing with a large T piece. The second limb of the T bears a short piece of tubing which can be narrowed by a screw-clamp. The third limb is connected with the recording tambour. The screw-clamp is adjusted so that the lever-point makes the desired excursion. (In place of the screw-clamp, a hole may be cut in the tubing, which can be partly occluded by a piece of glass-rod inserted through the free end.) The anesthetic can be given by modifying the arrangement as in Fig 100.

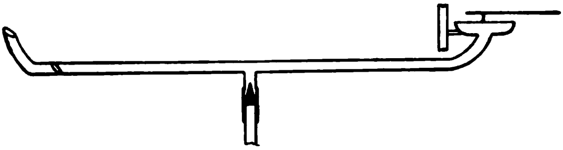

Fig. 114.— Simple trachea-tambour method.

(b) Trachea-Bottle-Tambour Method.— The arrangement is explained by Fig. 115. The bottle should be as large as possible (a five-gallon glycerin can or large jug answers admirably). The connection between the trachea and bottle should be as short and wide as possible. The vent is closed whenever tracings are taken, and opened between the tracings. The greatest care must be used to avoid asphyxia. It is advisable to disconnect the bottle occasionally, and blow air through it with bellows.

(c) Double Tambour (Stethograph) Method.— A large tambour or other elastic reservoir is tied firmly to the chest or abdomen. Its interior is connected to a recording tambour, with the interposition of a T piece, by means of which the tambours can be moderately distended.

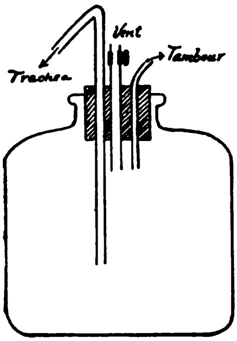

Fig. 115.—Respiration bottle.

The receiving tambour may be given various forms: An efficient instrument may be made by cutting of the top of a pound ether tin, a centimeter below the rim, tying a rubber membrane over this, and closing the stopper opening with a perforated cork, bearing a glass tube.

The sleeve of the sphygmanometer can be wound about the chest and connected with the recording tambour; or a piece of bicycle tire will answer the purpose.

(d) Lever Methods.—In these, the motion is transmitted to an ordinary muscle-lever (page 798). This may be done, (1) by taking a stitch through the skin and tying the string to the lever; (2) a small incision may be made through the skin and muscle, on the right side, about the lower edge of the diaphragm: The end of a glass rod or the bowl of a teaspoon is inserted between the liver and diaphragm and the handle connected with the lever. (3) A knitting needle may be thrust directly into the liver through the skin (danger of hemorrhage!). (4) A special lever may be used, bearing a rod which rests on the chest and abdomen. This does not require anesthesia. It is well adapted to obtaining tracings of the Cheyne-Stokes respiration in deep anesthesia.

The Volume of Respiration.— To measure this, the animal must be made to breathe through a valve which separates the inspired and expired air, the volume being estimated by a gas-meter, or by conducting the air into a spirometer (see Stewart's Manual).

Artificial Respiration.— This may be maintained in intact animals by alternate ryhthmic pressure on the chest and abdomen. Very little force should be used. In operated animals the artificial respiration is maintained through some mechanical apparatus connected with the tracheal cannula. The simplest device consists in a large *bellows* (15 × 22 inches, exclusive of the handles). This may be arranged for foot power by fastening a spiral upholsterer's "lounge spring No. 2" between the handles. The spout is closed with a cork. An inch hole is bored in the top. This bears a perforated cork, from which a tube leads to the tracheal cannula. A T piece is inserted in the course of this tube, the free limb of the T being closed when the air is driven into the lungs, and opened when it is expelled. This may be done with the finger, but it is better to employ some automatic device. The T piece may be placed directly in the cork of the bellows. The free limb is connected with a rubber tube which is tied to the handle, in such a fashion that it is stepped on and closed when the bellows are compressed (Fig. 116). (The spring may also be placed inside of the bellows.)

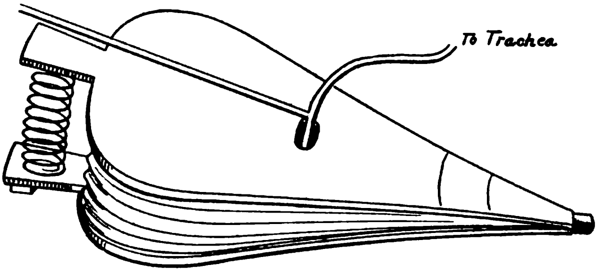

Fig. 116.— Bellows for artificial respiration.

R. E. Hall has perfected a simple valve for this purpose (Fig. 117). It consists of a metal T piece, with a steel plunger, well fitted and oiled, which is driven up by the bellows and falls back in expiration. The excursions are controlled by short pieces of rubber tubing, inserted in the brass.

In an emergency, the operator can inflate the lungs by blowing into the tracheal tube.

Artificial respiration should be performed at about the rate of the operator's own breathing.

The anesthetic may be continued during the artificial respiration by blowing the air through the Woulf's bottle, shown in Fig. 100 (taking care to have the level of the anesthetic so low that it cannot be projected into the tube). This requires considerable watching, so that it is better to employ the Gréhant anesthesia, if the experiment involves prolonged artificial respiration.

Cardiac massage is described in Exercise 58, No. 7.

Oncometers.— These are instruments for observing and measuring changes in the volume of organs. See description in Stewart's Manual, or Practical Physiology, Beddard, or Brodie's Experimental Physiology, etc. They can be obtained, for instance, from Palmer (see page 784). In working with excised organs, a simple apparatus will suffice. This may consist of a conveniently-shaped tin box, which has two openings, one for the vessels of the organ, another for the tube of the recording apparatus. This consists of an elongated thin rubber bag (such as is used in toy-balloons), connected with a water manometer. The bag is filled with water, connected with the manometer, and folded about the organ within the box. When the latter is closed, any change in the volume of the organ is communicated through the bag to the manometer. It may be recorded by connecting the free limb of the manometer with a Brodie Bellows. (For description of oncometers, see Roy, Schaefer, Edmunds.)

Circulation Time.— See Stewart's Manual.

Vein Pressure.— This lateral pressure in the inferior cava is measured by connecting the *central* end of the femoral vein with a manometer, shaped like the mercury manometer, but filled with water. A little water should be added from time to time, to make sure that the vein is not plugged by a clot. A tracing can be obtained by filling the manometer with half-saturated magnesium sulphate and connecting with a Brodie Bellows. With some care, a cork or hollow aluminum float and aluminum style can be fitted directly to the manometer.

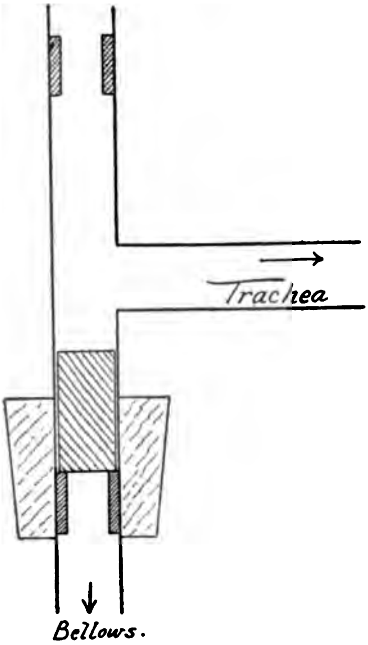

Fig. 117.— Hall's respiration valve. Natural size.

Vein Flow.— The blood of the animal must be defibrinated. An outflow tube is then introduced into the vein, terminally or by a T piece. The outflow is measured or counted; it may also be estimated by the rate of rise of a tambour (Barcroft and Brodie, 1905).

Drop-Marker.— This serves to register the rate of dropping (from ureter, vein, etc.) on a drum. An efficient form is constructed from a muscle lever, as in Fig. 118. The outflow tube is placed at least a foot over the little mica slide.

Myocardiograms.— These are taken with muscle-levers. The most convenient method consists in thrusting a knitting needle through the left thorax, a little above the apex beat, directly into the heart. This causes practically no disturbance in the circulation. Another knitting needle is tied securely to the long limb of a muscle-lever. The two needles are connected by a string. Raising the string on the heart needle, or lowering it on the lever needle, will increase the excursions. The best results are obtained by adjusting the string in the direction of the movement of the heart needle.

Tracings from the exposed heart are obtained by hooking a bent pin into the apex, and connecting with the lever (Fig. 119). The heart is exposed as on page 809; the pericardium is opened and stitched to the side of the chest, forming a little hammock in which the heart lies. The animal should be curarized.

Methods of isolating the heart are described in Exercises 48 and 74 to 76.

Perfusion Apparatus for Excised Organs.— The most convenient method, all things considered, consists in raising the reservoir itself to the desired level — 1 to 1½ meters above the organ. If the perfusion is to be made *at room-temperature*, so-called mercury bulbs, of the form shown in Fig 102, or "Aspirator" bottles (having an opening near the bottom) are most convenient. They have a capacity of ¼ to 2 Liters. If a constant pressure is desired, the upper opening is closed with a Mariotte stopper, a perforated stopper, bearing a glass tube which dips to near the bottom of the bulb. A tube, consisting of alternating sections of rubber and glass and bearing a pinch-cock, passes to the organ, which is conveniently arranged on a little bench. A T piece is inserted between the tube and the cannula. The free limb of the T is clamped. It serves for removing air, or for connecting a second reservoir, if the solution is to be changed (Sollmann,

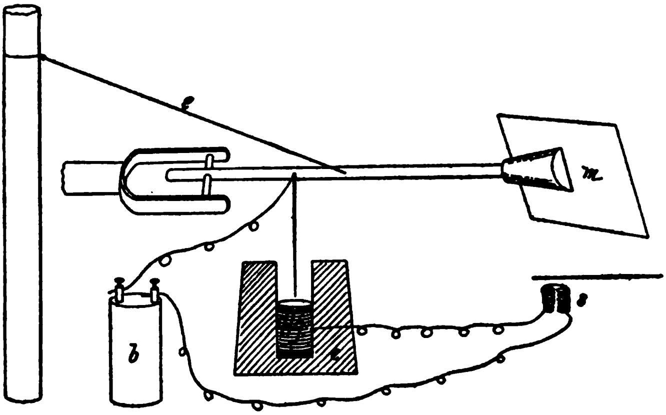

Fig. 118.— Drop Marker: A small mica slide *m* is fixed at the end of the muscle-lever by means of a small cork. The mica slopes downward. The lever is kept horizontal by a long band of thin elastic rubber *e*, so that a drop falling on *m* will cause the pin *p* to dip into the mercury in the hollow cork *c*, closing the circuit with the battery *b*, and moving the magnet *s*, which writes on the drum.

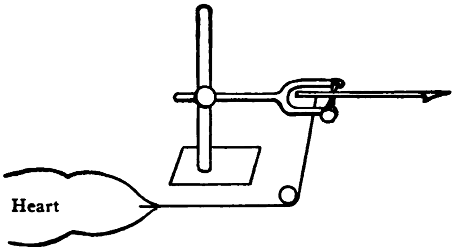

Fig. 119.— Myocardiograph.

1905). To prevent drying, the organ may be covered with a flap of muscle and skin, cut from the abdominal wall of the dead animal.

If *warm fluid* is to be used, a large bottle with siphon is used as reservoir, and placed in a water bath at the desired temperature. The bulb of a thermometer is fixed in the T. The organs are supported by cotton, or laid in a bath of warm oil, or suspended, in a hot-water funnel (such as is used for filtering gelatin). This allows good drainage.

Preparation of the Organ for Perfusion.— The animal is usually bled. (If the perfusion is to be made with diluted blood, a liter or two of Locke's Solution (see Index) is run into the femoral vein and the animal is again bled.) The bloods are defibrinated by whipping, strained through cloth, and poured into the reservoir. The organ is exposed, a cannula is tied in its artery, and connected with the reservoir. The vessels are well flushed (to prevent clotting). The vein cannula is now tied in. All other vessels are tied and the organ is removed. To avoid drying, it may be covered with a muscle-skin flap from the abdomen of the dead animal.

Taking the Temperature of Animals.— This is generally taken in the rectum. In working with small animals, the bulb of the thermometer should be warmed in the hand, and oiled, before it is inserted. The thermometer should always be pushed in for the same distance, which may be marked on the stem. The mercury must be completely covered.

Collection of Excreta.— Catheterization requires considerable practice in dogs, and in female rabbits; it is very easy in male rabbits. A No. 5 bone-tipped gum male catheter is used. The urine of rabbits may be collected by *expression:* The animal is grasped firmly in the left hand, so as to push the abdominal organs toward the pelvis, when moderate pressure with the right hand, over the bladder, usually accomplishes the desired result. The urine and feces may also be collected by placing the animals in suitable "*Metabolism cages.*"

Diabetes Puncture and Heat Puncture.— See Stewart's Manual, or Practical Physiology, Beddard, etc.

Peristalsis.— The movements of the intestine may be watched in situ, or after excision; pieces of the intestine being laid or suspended in oxygenated Locke's fluid, with or without the addition of defibrinated blood (see Exercise 46). Tracings may be obtained by attaching the excised pieces to muscle-levers, keeping them immersed in the fluid. Further details are given in the papers of Magnus (Pflüger's Archiv, vol. 108, p. 1, 1905).

The movements of the intestinal contents can be observed in intact animals by Canon's method, mixing some bismuth with the food, and observing with the fluoroscope.

V. DRUGS COMMONLY USED IN EXPERIMENTAL TECHNIC.

The proper doses are found in the Dose Tables, Chapter XXXIX.

Anesthetics: See page 801.

Apocodein: Paralysis of endings.

Apomorphin: Emetic.

Atropin: Paralysis of endings of vagus and sympathetic.

Barium Chlorid: Stimulation of smooth muscle.

Cocain: Local paralysis of nerves.

Curare: Paralysis of endings of striped muscle; immobilization. (Remember that sensation is not abolished!)

Diuresis: Caffein, Theobromin, Normal Saline, Matthew's Solution.
Fever: See Exercise 36.
Fluorid of Sodium: Protoplasmic poison.
Glycosuria: See Exercise 34.
Leech Extract or Peptone: To render blood non-coagulable.
Morphin: To prevent vomiting; anesthesia.
Muscarin: Stimulation of endings (antagonist to atropin).
Nephritis: See Exercise 33.
Nicotin: Paralysis of ganglia.
Nitrite (Amyl): Fall of blood-pressure.
Pilocarpin: Stimulation of endings, particularly glands.
Strychnin: Convulsions.
Suprarenal: Stimulation of sympathetic endings; particularly vasoconstriction, rise of blood-pressure.

PERFUSING SOLUTIONS.

These solutions are practically indifferent to the tissues for which they are used.

The following are the more important:

Normal Saline Solution.—Sodium chlorid solutions, containing 0.75% for frogs, 0.9% for mammals.

Ringer's Solution (for frogs) consists of:

$NaCl$ 0.7%;—KCl 0.03%;[1]—$CaCl_2$ 0.026% (crystals).

It is convenient to keep a *stock solution* of 20 times this strength on hand:

$NaCl$ 14 Gm.;—KCl 0.6 Gm.;—$CaCl_2$ 0.52 Gm. (crystals);—Water to 100 c. c.

Add 5 c. c. to 95 c. c. of distilled water.

Locke's solution (for mammals) consists of:

$CaCl_2$	0.024% (crystals)
KCl	0.042%
$NaHCO_3$	0.03%
$NaCl$	0.9%
Dextrose	0.1%

Stock solutions:

A:	$NaHCO_3$	3.0 Gm.	**B:**	$NaCl$	90 Gm.	**C:**	$CaCl_2$	2.4
	KCl	4.2 "		Water	to 1,000 c.c.		Water	to 100 c.c.
	Water	to 100 c.c.						

D: Dextrose: 1 Gm. packages.

For use, add 10 c. c. of A and 100 c. c. of B to 900 c. c. of water. Shake. Add 10 c. c. of C and a gram package of dextrose. A stream of oxygen is kept bubbling through the liquid.

Ringer-Locke Solution (for mammals) is Locke's solution with the omission of the dextrose.

Ringer-Langendorff Solution (for mammals) consists of:

$NaCl$ 0.8%;—$CaCl_2$ 0.01%;—KCl 0.0075%;—$NaHCO_3$ 0.01%.

S. A. Matthews' solution for diuresis (mammals):

$NaCl$ 3.67 Na_2SO_4 10.1 NaCitrate 3.36 $CaCl_2$ 0.136
Water to 1,000.

Solutions of Salts giving the same freezing point as 1% Sodium Chlorid (1 Gm. of NaCl added to 100 c. c. of distilled water; $\Delta =$ 0.589; molecular concentration $=$ 0.316).

All the salts are to be weighed in grams and made up to 1 Liter with distilled water. They should first be *dried* to constant weight at 110° C., unless otherwise stated. They must always be controlled by actual freezing point determination (see Exercise 23).

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[1] 0.01% gives a more rapid rate of the heart.

Checked by the Author:	
$BaCl_2$	25.62
$CaCl_2$	16.33
HCl	10 c.c. = 15.8 c.c. $n/_{10}$ NaOH
LiCl	7.26
$MgCl_2$	21.15
NaAcetate	12.75
$NaHCO_3$ (Do not dry)	9.66
$NaClO_3$	17.95
NaCitrate (47.33 to 75.73 crystals)	27.37
$NaNO_3$	15.35
NaOxalate	23.0
Na_2HPO_4	21.0
Na_2SO_4 (47.73 crysatls)	21.0

Deduced from Published Tables:	
Alcohol plus 1 Liter	14.50
Cane Sugar plus 1 Liter	108.82
Glucose plus 1 Liter	56.74
Urea plus 1 Liter	18.94
$MgSO_4$	35.37
Na_2CO_3	14.54
NaOH	7.00

Deduced by Analogy:	
NH_4Cl	9.13
NaBr	17.46
NaI	25.42
NaCNS	14.24
NaF	7.21

CHAPTER XXXV.

CHEMIC EXERCISES.

Introductory Remarks.— Before beginning on the laboratory work, the student should check the contents of his locker and familiarize himself with the reagents on the shelves (see Tables XVII to XXII, pages 780 to 784). These are arranged alphabetically. Remember that they are to be replaced in their proper position as soon as used. The student should supply himself with towel, soap, matches, scratch-pad, and dissecting instruments. He should keep his working-place clean and neat.

The experiments, explanatory remarks, and references should be assigned and read before coming to the class. Cross-references to other experiments (*e. g.*, "Consult Exercise so and so") mean that these experiments are to be read, but not to be performed, at this time. The references to the chapters of the text-book may be neglected by the student. The student should reflect on the object and conclusions of the experiment whilst it is in progress. He should take account of all the experiments performed in the course, including those shown as demonstrations or assigned to other members of the class. Two students may collaborate in the chemic experiments.

If an experiment is unsuccessful, it should be repeated. In the event of a second failure, the student should call on the demonstrator for help. *Every unusual or atypical result should be reported.*

Additional apparatus is furnished on written requisition. The special material needed for each experiment is noted at the bottom of each page (*S. M.*).

General Remarks on Note-Taking.— The results of the experiments should be entered briefly in a special note-book. The method should be indicated sufficiently to make the notes understandable. Tracings should also be inserted, either the original, or copies taken free hand, with tracing-paper, or blue prints.[1] Unnecessary detail is to be avoided. It is all but impossible to enter these results neatly at the work-table or in the conference; it is therefore better to jot down the notes on scratch-paper, and to transfer them to the note-book when the practical work is completed. The results should be followed by a brief statement of the conclusions which may be drawn from the experiment. These should only bear on principles, not on details. They should go no farther than the data of the experiment warrant. With the animal experiments, it is better to wait with the drafting of the conclusions until the results of the entire class have been collected and discussed.

Specific modifications of these general directions are mentioned in individual experiments.

As the work on each drug is completed, a summary of the action should be entered in Chapter XXXVIII, as indicated at the end of the Exercises (see for instance Exercise 24, p. 861).

EXERCISE 1.— PHARMACOGNOSY.[2]— GROSS ANATOMY OF VEGETABLE DRUGS.

To precede Chapter I. (No notes required.)

Conference and demonstration of dried parts of plants to illustrate: *Roots* (Belladonna, Sarsaparilla, Phytolacca, Ginseng); *Rhizomes* (Podophyllum, Calamus, Aspidium); *Tuber* (Aconite, Jalap); *Bulb* (Squills); *Herb* (Peppermint); *Cortex* (Cinchona, Wild Cherry); *Leaves* (Senna, Digitalis); *Flowers* (Rose, Cloves); *Fruits* (Fennel, Cubeb, Cardamom Colocynth); *Seed* (Flaxseed); *Excrescence* (Nutgall); *Exudations* (Opium, Aloes, Asafetida, Acacia, Copaiba).

EXERCISE 2.— PHARMACOGNOSY, CONTINUED.— PLANT HISTOLOGY.

Study in connection with Chapter I. The student should make drawings of the sections, if time permits (optional). No other notes are required.

Demonstration of sections showing: *Calcium oxalate crystals* (Rhubarb, Squills, and Solomon's Seal); *Starches* (Wheat, rye, potato, corn, rice, oats, ginger — shows also resin cells,— aconite); *Aleuron grains* (Castor bean); *Spiral vessels* (L. S.[3] Podophyllum); *Dotted vessels* (L. S. and T. S. Glycyrrhiza); *Pitted wood cells* (L. S. Pine wood); *Stone cells* (T. S. Cascara Sagrada); *Parenchyma cells* (T. S. Cypripedium); *Bast cells* (Cinchona, Cascara Sagrada, and Sassafras bark); *Fibro vascular bundles* and *epidermis* (T. S. Podophyllum); *Cork cells* (T. S. Common cork); *Stomata* (Leaf epidermis); *Hairs* (Mullein leaf, T. S. Sarsaparilla root); *Resin cells* (T. S. Calamus); *Oil spaces* (T. S. Clove); *Resin duct* (L. S. Tamarack); *Pollen* (Pine); *Spores* (Lycopodium).

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[1] See page 794.

[2] For more comprehensive work on Pharmacognosy, Exercises I to III, see Hatcher & Sollmann, Text-book of Materia Medica, Saunders & Co., 1904.

[3] L. S.= longitudinal section; T. S.= transverse section.

S. M., Ex. 1: Specimens.

S. M., Ex. 2: Mounts, Microscope, Diagrams.

EXERCISE 3.— PHARMACOGNOSY, CONTINUED.— GENERAL REACTIONS OF PLANT CONSTITUENTS.

Study in connection with Chapter I.

(It is assumed that the student is familiar with the characters of glucose, cane-sugar, starch, proteids, and fats. Should this not be the case, they should be studied before the following experiments are made.) Two students may work together, if desired. Make notes on the results.

I. Alkaloids.[1]— 1. *Alkalinity.*— Place a drop of 1% nicotin on red litmus paper: blue color.

2. *Precipitation Reactions.*— Place on slides a few drops of 1 : 1,000 acidulated quinin sulphate solution, mix with a drop of the following, and note the amorphous precipitates:

(*b*) Iodin in KI = White.
(*a*) Mercuric Potassium Iodid = Reddish.
(*c*) Picric Acid = Yellow.
(*d*) Tannin (1%) = Gray.
(*e*) Phosphotungstic Acid[2] = White.

3. *Solubility Characters of Alkaloids and their Salts.*— In a test-tube make about 5 c. c. of an acidulated 1 : 1,000 solution of quinin sulphate distinctly alkaline by NaOH solution: a precipitate of free alkaloid is thrown down (free alkaloids are generally insoluble in water, whilst their salts are soluble). Add about 10 c. c. of ether and shake with a gentle rotatory motion. Draw off the ethereal solution from the top with a pipette, and again shake the watery solution with 5 c. c. of ether. Again draw off the ether. Acidulate some of the remaining watery solution and test it with mercuric potassic iodid, observing that there is no or very little precipitate (the free alkaloid being completely extracted by the ether). Shake the ethereal solution with some dilute sulphuric acid. Draw off a little of the acid solution from the bottom, and test with mercuric potassic iodid: a precipitate occurs. (The acid converted the quinin into the sulphate, which is soluble in water, and insoluble in ether.)

4. *Lassaigne's Test for Nitrogen.*— Place a knife-pointful of dry quinin sulphate in a dry test-tube. Take a piece of metallic Na, size of small pea, dry with blotting-paper, and add to quinin. Heat red hot and plunge into beaker with a little water. Filter. Add a few drops $FeSO_4$. Let stand five minutes. Acidulate with conc. HCl and heat: Greenish or blue color or precipitate of Prussian Blue.

Note the peculiar odor of quinolin (compare with bottle on desk), a decomposition product of quinin.

5. *Microchemic Reactions.*[3]— Alkaloidal precipitates often present a crystalline character, which may be useful in their identification. This is illustrated by the following examples. (Mix the solutions on a slide, and examine from time to time with low-power microscope, until typical crystals are seen. Make drawings.)

(*a*) 5 drops of 2% Morphin Sulphate and one drop 10% NH_4OH: rapid formation of needles. (Rub with a glass rod, if necessary).

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[1] Similar reactions are given by other organic bases, *e. g.*, pyridin and quinolin (see first edition, page 769).

[2] *Phosphotungstic Acid:* A 10% solution in 4% HCl.

[3] These reactions may be demonstrated.

S. M.— Waterbath, slides, and covers.

(*b*) 5 drops of $^1/_{10}$% Nicotin and excess of picric acid: at first a fine precipitate; later stellate crystals.

(*c*) Substitute 1% Atrophin Sulphate for Nicotin in (*b*): feathery crystals and stellate groups.

(*d*) 1% Strychnin Sulphate and potassic bichromate sol.: fine rosettes of needles at once.

II. Glucosids.— (These yield glucose as one of their decomposition products. *Salicin* is an example.)

6. Test a little fresh 1% solution of Salicin for sugar by Trommer's Test: negative.

7. *Decomposition by Acids.*— To another portion of the solution add ⅕ volume of 5% sulphuric acid; boil in water bath for 10 minutes; make alkaline with NaOH, and apply Trommer's: positive.

8. *Decomposition by Ferments.*— To another portion of the solution add some saliva and heat in water bath at 40° C. for half hour; test for sugar: positive.

9. Note difference in sweetness of alkaline and acidulated fluid-extract of Licorice. (The sweet glucosid, glycyrrhizin, is precipitated by acids.)

III. Saponins.[4]—

10. *Foaming.*— Shake a few drops of a tincture of soap-bark (which is rich in saponin) with a little water: considerable foam is produced, which subsides slowly.

11. *Emulsification.*— Add 25 drops of the soap-bark tincture to about an inch of cotton-seed oil. Shake. Add an inch of water and shake: a smooth mixture (emulsion) is formed. Add alcohol: the emulsion persists.

12. Sapotoxins lake blood (consult Experiment 22 A).

IV. Anthraquinon Derivatives.— (Cathartic Emodin Principles).

13. To an infusion of rhubarb add a few drops of NaOH: red color.

V. Tannins.—

14. *Tannic Acid.*— (Dissolve a little tannin in hot water or use the 1% solution).

(*a*) Add drop of Fe_2Cl_6: green-blue-black color. Dilute until it is transparent. Add a few drops of NaOH: garnet color. Add cautiously an excess of H_2SO_4: greenish-red; with more, greenish-yellow.

(*b*) Add some $Pb(C_2H_3O_2)_2$: large white precipitate. Add NaOH and shake: pink.

(*c*) Add some NaOH: reddish-brown color.

(*d*) Observe that tannin precipitates alkaloids (*e. g.*, quinin); proteids (egg-white solution); and gelatin.

(*e*) Add a drop of Fe_2Cl_6 to a little *infusion of Cinchona* (greenish color). The tannins occurring naturally in plants give a greenish color with iron; tannins occurring in pathologic formations (nutgalls) give a bluish color.

15. *Gallic Acid.*— To a 1% solution of gallic acid add a few drops of 1% KCN: a red color appears, which soon fades, but reappears on shaking (Young's test). Pure tannic acid does not give this reaction.

VI. Gums.— (Use a 10% solution of Acacia.)

16. (*a*) *Inversion by Acids.*— Test for sugar: negative. Add ⅕ vol. of 5% sulphuric acid, and boil for 10 minutes in water bath. Make alkaline with NaOH, and test for sugar: positive. This test is given in common by gums, starch, glucosids, and other carbohydrates.

(*b*) Add some *alcohol: precipitate* (difference from glucosids). *Borax* also causes precipitation.

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[4] For a specific color reaction, see first edition, p. 771, No. 37.

(*c*) Add a few drops of ***iodin*** solution: no blue color (difference from starch).

VII. Resins.— (Use commercial rosin.)

17. *Solubility.*— Note that this is soluble in alcohol, but is precipitated from this solution by adding water. It is also soluble in ether, turpentine, oil, and boiling sodium hydrate solution, but insoluble in gasolin.

VIII. Volatile Oils.— (Use spirits of turpentine.)

18. (*a*) *Solubility.*— Note that this mixes with alcohol, ether, gasolin, and cotton-seed oil, but not with water.

(*b*) Note that it makes a ***greasy stain*** on paper, but that this stain disappears in time, especially on heating.

IX. Coloring Matter.—

19. *Chlorophyll.*—

(*a*) Note the green color of a fresh tincture of lettuce leaves.[1]

(*b*) Add some dilute HCl: yellow color.

(*c*) To another portion add some NaOH: the color becomes an old gold-green. (Chlorophyll has a characteristic spectrum, in which the above reagents produce definite changes; see Hatcher and Sollmann; Materia Medica.)

20. *Curcuma* (*Turmeric*).—

(*a*) To some of the 1% tincture add a drop of NaOH (reddish-brown color); then an excess of dilute HCl: yellow color is restored.

(*b*) Dip some paper which has been dyed with curcuma (Turmeric Paper) into 5% boric acid: orange color. Touch it at one place with dilute HCl and dry: deeper red. Moisten with ammonia: deep blue. (This serves also as a test for boric acid.)

21. *Cochineal.*— Triturate a single insect with about 10 c. c. of water; notice the tint; add 20 drops of ammonia: the color deepens. Filter; add excess of dilute HCl: the color becomes lighter and there is a precipitate of carmin; add excess of ammonia: the carmin redissolves and the color deepens again.

22. *Cudbear.*— Add 5 drops of Tr. Persionis to about 5 c.c. of water; add a few drops of dilute HCl: note the change of color (lighter tint); add excess of NaOH: bluish violet color.

Note.— The origin of red colors may be discovered by the addition of NaOH; this causes a change to green if the pigment is that of fruits; to blue or purple, if it is of other vegetable origin. Anilin dyes are not changed. For other tests, see La Wall, 1905.

Optional.— Study a series of *starches* with the high power of the microscope, and make drawings (see Fig. 1, T. B.).

Conclusions.— From your own experimental results, formulate definitions for: Alkaloid; Glucosid; Saponin; Tannin; Gum; Resin; Volatile Oil.

EXERCISE 4.— METROLOGY.

To precede Chapter II.

Conference and Demonstration of: Decimeter cube, meter, types of balances, sets of metric and apothecary weights, conic and cylindric graduates (metric and wine); measuring flask, pipettes, burettes, picnometer, areometer, thermometers, method of taking specific gravity of solids; methods of measuring and weighing.

No notes required. Work out some examples in metrology.

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[1] Some fresh lettuce is bruised in a mortar with sand, triturated with alcohol, and filtered.

S. M., Ex. 4: Apparatus for demonstration.

EXERCISE 5.—PHARMACEUTIC METHODS.

To precede Chapter III.

Conference and demonstration of: Mortars; desiccators; different forms of baths and ovens; of stills; percolation; use of separatory funnel; powders of different degrees of fineness; suppositories.

No notes required.

EXERCISE 6.—PHARMACEUTIC MANUFACTURING.[1]

Study in connection with Chapter IV.

Manufacture of the following preparations (U. S. P. or N. F.):

Aqua Menthæ Pip.; Aq. Chlorof.; Liq. Chlori Comp.; Liq. Pot. Arsen.; Liq. Calcis; Liq. Ammon. Acet.; Liq. Magnes. Citr.; Liq. Plumbi Subac.; Liq. Ferri Chlor.; Dobell's Solu.; Muc. Acaciæ; Spir. Camph.; Sp. Ammon. Arom.; Sp. Menth. Pip.; Glyc. Boro glyc.; Pyroxolon; Collodion; Coll. Flex.; Infusum Sennæ Co.; Inf. Digit.; Decoct. Cetrar.; Tinctura Digit.; Tr. Opii; Tr. Ferri Chlor.; Tr. Opii Camph.; Acetum Scillæ; Fluidext. Aconiti; Ext. Ergotæ; Syrupus Prunis Virg.; Syr. Ferri Iod.; Syr. Ac. Citr.; Elixir Arom.; Oleoresina Capsici; Mist. Cretæ Co.; Lotio Nigra; Lot. Flava; Lot. Plumbi et Opii; Emuls. Ol. Morrhuæ; Em. Chloroformi; Em. Asafœtidæ; Sapo Mollis; Linim. Saponis; Lin. Calcis; Lin. Terebinth; Lin. Ammonia; Pulv. Efferv. Co.; Pulv. Glycyrrh. Co.; Caff. Citr. Efferv.; Pil. Hydrarg.; Massa Ferri Carb.; Gelatin, sugar, and chocolate-coated pills; Supp. Ac. Tann.; Unguentum; Ung. Zinci Oxid; Ung. Aquæ Rosæ; Ceratum; Empl. Plumbi; Empl. Adhesinum; Empl. Belladonnæ; Resina Podophyl.; Ac. Boric; Sod. Citr.; Lac. Sulphur.

EXERCISE 7.—DISPENSING.

The experiments will be demonstrated, and are to be repeated by each student; the products must be checked by the demonstrator. The solids may be weighed in advance, if scale facilities are limited. No notes required. Study in connection with Chapter IV.

Experiments.—

1. Fold a plaited and a plain *filter,* properly trimmed (Fig. 120).

The former is made by folding a square or round sheet of filter-paper along the line 1, *a;* and this piece again in the same way along 2, *b*. If square, the corner is trimmed off along the dotted line 3, *a*. The filter is then placed in the funnel, opened, and moistened with water or a little of the liquid to be filtered.

The plaited filter is started like the plain. The fold 1, *a* is made; 2, *b* is here only a crease. The paper is flattened again as in 2, and the edges folded in as in 3, *b*. The paper is again laid out flat and each eighth furnished with an extra crease, as in 4; first as in *a*, then folding over *c*, and then making *b*. The paper, flattened out, shows creases as the lines in 5, all in the same direction. Each space is now folded back along the dotted line in the opposite direction, as in making a fan (6). The numbers in (6) refer to the order in which the creases are made. If this is separated, it gives the figure 7.

The creases should not be carried sharply to the point, but should be quite light for ¼ to ½ inch from the end, to prevent breaking.

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[1] **This exercise may be made optional. Detailed notes should be kept.**

S. M., Ex. 5: Apparatus for demonstration.

S. M., Ex. 7: (for twelve students).—Balance and weights; 30 papers for folding filters; 15 stiff papers for plasters; powder papers; 120 gelatin capsules, No. 2.

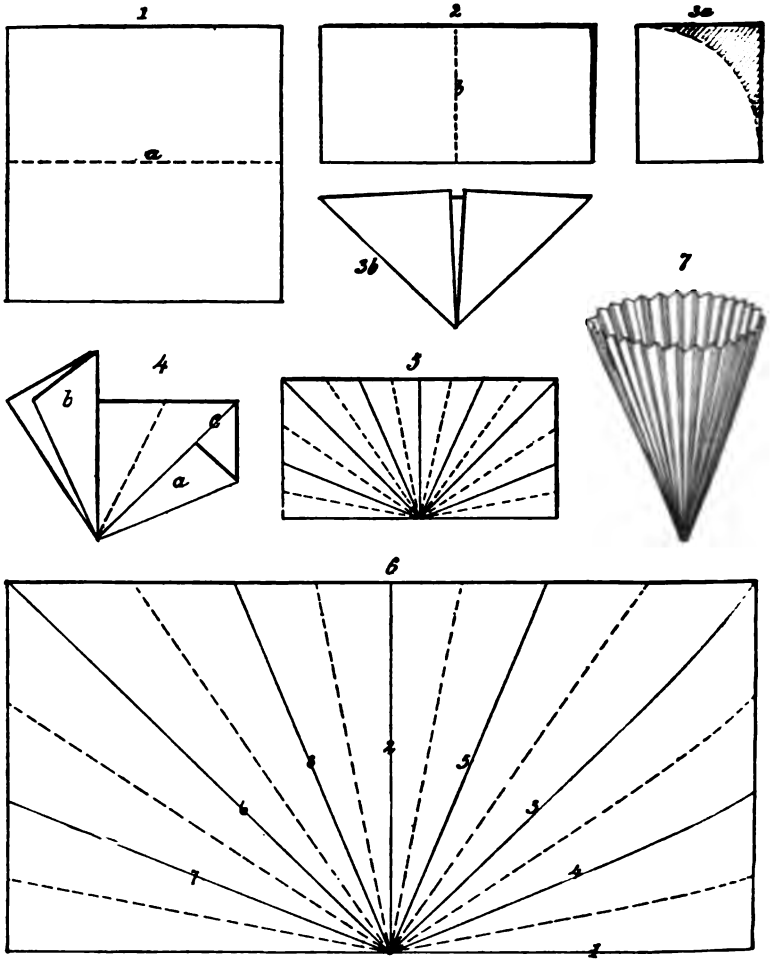

Fig. 120.— Methods of folding filters.

2.	*Solution:*	℞. Sodii Chloridi	1.
		Sacchari	5.
		Inf. Menth. Pip.	20.
		Mix and dissolve.	
3.	*Powder papers:*	℞. Hydrarg. Chlor. Mitis	1.
		Pv. Amyli	5.
	Mix and divide into 10 powders, properly folded.		
4.	*Capsules:*	℞. Pv. Amyli	2.
		Fill into 10 capsules.	

5. *Emulsion:* ℞. Ol. Morrhuæ .... 5.
Pv. Acaciæ .... 2.
Aquæ .... 5.

Make emulsion (Rub the acacia with the water and add the oil at once, triturating vigorously). When the emulsion is formed add 50 c. c. of water, and shake: The oil remains emulsified.

6. *Ointment:* ℞. Pv. Amyli .... 1.
Petrolati .... 10.

Mix and make into ointment. This must be free from lumps.

7. *Pills:* ℞. Pv. Glycyrrh. .... 2.
Make into 10 pills.

8. *Plaster:* Spread a plaster, 5 × 6 inches.

Optional.— This exercise can be profitably extended as much as time will permit, the student writing and dispensing a series of prescriptions. These will very likely illustrate some of the incompatibilities.

EXERCISE 8.— INCOMPATIBILITIES.

The student should state in his notes the results, the general rule which each experiment illustrates; and, if possible, the chemical reaction which takes place, and the nature of the precipitate, etc.

Study in connection with pages 74 to 79.

Experiments.— I. Explosives.—

1.[1] Rub a little chlorate of potash and tannin in a mortar: detonation.

2.[1] Mix some strong nitric acid and alcohol in a beaker, and let stand in a bell jar: in a short time orange vapors arise, and suddenly the solution boils up and is thrown from the beaker.

3. Mix some concentrated sulphuric acid and water in a test-tube, and notice the evolution of heat.

II. Incompatibility by Oxidation.—

4. $Kr_2Cr_2O_7$ solution + Alcohol; no change. (There may be a slight precipitate, which redissolves if a little water is added.) Add conc. H_2SO_4. Green color, and evolution of gas.

$$[K_2Cr_2O_7 + H_2SO_4 = 2CrO_3 + 2KHSO_4 + H_2O$$
$$CrO_3 + 3C_2H_6O = Cr_2O_3 + 3C_2H_4O \text{ ('aldehyd)} + 3H_2O$$
$$C_2O_3 + 3H_2SO_4 = Cr_2(SO_4)_3 + 3H_2O]$$

5. ℞. $KClO_3$ 0.5
Aquæ .... 10.
Glycerini .... 2.
Tr. Ferri Chlor.... 1.

If put up without heating, no change will occur, illustrating the possibility of mixing certain explosives in solution.

6. Conc. HCl + dry $KClO_3$ + heat: Evolution of Chlorin Gas: liquid turns golden or canary color.

$$(2HCl + KClO_3 = KCl + ClO_2 + Cl + H_2O.)$$

7. H_2O_2 + KI (let stand) = Yellowish-brown color.

$$(2KI + H_2O_2 = 2KOH + I.)$$

8. KI + $KClO_3$ + HCl (heat) = Brownish color.

$$(KI + KClO_3 + 2HCl = 2KCl + ClO_2 + H_2O + I.)$$

9. ℞. Solution KI
Spir. Æth. Nitr.

Brown-red color; liberated iodin.

III. Chemic Incompatibility by Precipitation.—

10. $FeSO_4$ + (*a*) NaOH = Green precipitate.
(*b*) Na_2CO_3 = Green precipitate.

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[1] Demonstration; not to be done by students.

S. M.— Expts. 1 and 2.

(*c*) Pot. Oxalate (let stand) = Yellowish-white precipitate.
(*d*) *Sod.* Borate (let stand) = Greenish precipitate.
(*e*) Na_2HPO_4 = Grayish-white precipitate.
(*f*) Tannin = Dark blue.
(*g*) Infusion Uva Ursi = Dark bluish-green.
(*h*) Infusion Cinchona = Dark green.

11. Fe_2Cl_6[1] + (*i*) Albumin = White precipitate.
(*k*) Acacia = Brown gelatinous precipitate.
(*l*) Sodium Salicylate = Reddish-purple color.
(*p*) Carbolic Acid (5%) = Bluish-violet color.

12. $CuSO_4$ + (*a*) = Greenish-blue precipitate.
(*b*) = Bluish-white precipitate.
(*i*) = Bluish-white precipitate.

13. $Pb(C_2H_3O_2)_2$ + (*i*) = White precipitate.
(*m*) NaCl = White precipitate.
(*n*) KBr = White precipitate.
(*o*) Na_2SO_4 = White precipitate.
Tinctura Opii = Brown precipitate.

14. $MgSO_4$ + (*a*), (*b*) = White precipitate.

15. $Ca(OH)_2$ + (*c*), (*e*) = White precipitate.

16. $HgCl_2$ + (*q*) $Ca(OH)_2$ = Yellow to brown precipitate.
(*r*) $FeSO_4$ + heat = Blackish-brown precipitate.
$[3HgCl_2 + 4FeSO_4 = Fe_2(SO_4)_3 + Fe_2Cl_6 + Hg_2SO_4 + Hg.]$
(*s*) KI; when red precipitate forms, add more KI, and it should redissolve.
(*i*) = White precipitate.

17. $AgNO_3$ as 13 (*i*), (*m*) and (*n*).

18. Saturated solution Quinin Sulphate + (*a*), (*b*), (*f*) = White precipitate.
(*t*) + Iodin solution (I + KI) = Brown precipitate.
(*u*) + Picric Acid = Yellow precipitate.
(*v*) + Pot. Merc. Iodid = White precipitate.

19. 1 : 100 Strychnin Sulph. + saturated KBr = Precipitate of crystal needles, increasing on standing.

20. ℞. Solution. Strych. S.
Solution. Pot. Iodid. } White crystalline precipitate.

21. ℞. Solution. Quinin. Bisulph.
Solution. Sodii Salicyl.
āā partes æquales. } White precipitate.

22. ℞. Solution. $HgCl_2$
Solution. KI } Red precipitate.
Continue addition of KI to solution, then add:
Tincturæ Cinchonæ: Brownish precipitate.

23. ℞. Solution. $AgNO_3$
Aquæ Font. (tap water) } White precipitate on standing, darkening in the light.

IV. Chemic Incompatibilities without Precipitation (compare also I and II):

24. Chloral + NaOH : Odor of Chloroform.
$(CCl_3COH + NaOH = NaCHO_2 + CHCl_3.)$

25. ℞. Ac Sulphur. Dil. gtt. 30.
Mist. Cretæ ...... 10 c. c. } Evolution of CO_2 and precipitation of $CaSO_4$.

26. ℞. Bism. Subcarb. 1
Liq. Pepsini .... 10 } Evolution of CO_2.
(Liquor Pepsini contains HCl.)

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[1] Tincture.

V. Pharmaceutic Incompatibility.—

27. H_2O to Tincture Guaiac } = White precipitate. } Resin.
H_2O to Spirits Camphor } = White precipitate. } Camphor.
H_2O to Tincture Cinchona = Brown precipitate. Resin.

28. ℞. NaCl 1
Aquæ 5
Tincturæ Cinchonæ... 5
} Brown precipitate (NaCl and resin).

29. Alcohol + (*i*) and (*k*) = White precipitate.
Alcohol + saturated solution NaCl = White precipitate. Add water: Redissolves.

30. ℞. Ac. Carbol. liq...gtt. 20.
Aquæ ....10 c. c.
Ft. solution.
(How can this be brought into solution?)

31. ℞. Tincturæ Ferri Chlor.
Tincturæ Cinchonæ
} Greenish-brown precipitate of iron tannate.

EXERCISE 9.—ISOLATION OF FIXED ORGANIC PRINCIPLES (ASSAYING).

Study in connection with Chapters IV and V, pages 73 and 84 to 86.

I. Isolation of Alkaloids.— (Nux Vomica.)

This experiment (a modification of the Stas-Otto method) is intended to illustrate the principles employed in isolating alkaloids and glucosids from organic mixtures, such as plants, stomach contents, organs, etc. Two students may work together. This is the method generally used for the isolation of organic poisons in toxicologic analysis. It rests on the different solubility of the constituents of the mass in successive solvents. It may be represented diagramatically as follows:

Extraction with boiling dilute tartaric acid.

Solution: Evaporation and extraction with alcohol, — Residue: Coagulated Proteid, Fiber, Fat.

Solution: Evaporation of alcohol and extraction with water, — Residue: Salts, proteids, fats.

Extraction of acid solution with ether, — Residue: Resins, fats, volatile oils, croton oil, chlorophyll, etc.

Addition of ammonia to watery solution, liberation of alkaloid, extraction with ether. — Ethereal Layer: Neutral principles, glucosids, cantharidin, caffein, and some other alkaloids.

Acidulation, alkalinisation with ammonia, extraction with acetic ether, chloroform, or hot amyl alcohol. — Ethereal Layer: Bulk of alkaloids.

Watery Layer: Inorganic Poisons. — Ethereal Layer: Morphin.

Record your observations in every step of the process.

1. *Extraction.*— To a mixture of 30 Gms. of hashed meat and 3 Gms. of powdered nux vomica add about 100 c. c. of water, and a pinch of tartaric acid. Boil for ten minutes. Cool. Strain through Canton flannel. Reject the solid residue.

2. *Removal of Salts, Proteids, and Fats.*— Add about 10 Gms. of sand to the strained solution, and evaporate, first on a free flame, then on water bath, to a paste. Add 40 c. c. of 95% alcohol, let stand 10 minutes or longer, with frequent stirring; and filter. The salts, proteids, and fats are left on the filter, since they are insoluble in alcohol. These are rejected. The alcoholic solution contains the organic poisons.

3. *Removal of Resins, Fats, etc.*— Dilute the alcoholic solution with an equal volume of water. This precipitates the above impurities (active resins and croton oil would be found in this precipitate). Filter. Reject the precipitate. Evaporate to near dryness, to remove the alcohol. Dissolve the residue in 50 c. c. of water. Filter. Assure yourself that the filtrate is acid.

4. *Removal of Neutral Principles and Some Other Impurities.*— Place the solution in a separating funnel, add 25 c. c. of ether, and shake with a gentle rotatory motion for ten minutes. Separate the two layers.[1] The ethereal layer would contain the neutral principles, which would be obtained by evaporating the ether. In the present instance, the ethereal layer is rejected. The watery layer contains the alkaloidal salts. It is treated by (5).

5. *Extraction of Alkaloids.*— Replace the watery solution of 4 in the separating funnel. Add ammonia until it is freely alkaline (this liberates the free alkaloids, which are soluble in ether. The alkaloidal salts are insoluble and were therefore not extracted in 4). Add 25 c. c. of ether and shake with a rotatory motion for 10 minutes. Let the liquid separate, and draw off the watery layer (which would contain morphin); this is rejected. The ethereal layer contains most of the alkaloids. Distill off the ether. Test some of the residue for Strychnin by Exercise 10, No. 1, *a;* and Brucin, Exercise 10, No. 1, *b;* dissolve another portion in a little dilute sulphuric acid, inject into a frog, and note the convulsions. (The ether extractions would be repeated, in practice, as long as they would take up any alkaloid.)

II. Alkaloidal Assay.— (Demonstration.)

The U. S. P. process for Belladonna is typical of the majority of assays (with the important exception of opium). It consists in a modification of Keller's method:

> Place 10 Gm. of Belladonna in an Erlenmeyer flask, and add 50 c. c. of a mixture of chloroform 1 part and ether 4 parts (both by volume). After inserting the stopper securely allow the flask to stand ten minutes, then add 2 c. c. of ammonia water mixed with 3 c. c. of distilled water, and shake the flask well at frequent intervals during an hour. Then transfer the contents to a small percolator which has been provided with a pledget of cotton packed firmly in the neck, and inserted in a separator containing 6 c. c. of norm. sulphuric acid diluted with 20 c. c. of distilled water. When the liquid has passed clear through the cotton, pack the Belladonna firmly in the percolator with a glass rod, rinse the original flask into the percolator with successive small portions (5 c. c.) of the chloroform-ether mixture, using in all 50 c. c. The separator should not be filled more than two-thirds. Next, shake the separator well for one minute, after securely

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[1] If the solution refuses to separate, proceed by footnote, page 833.

S. M., Nos. 1 to 4.— Meat mixture; Canton flannel, 1 ft. square (one for each two students); water baths; separatory funnels.

S. M., No. 5.— Still with water bath for Ether. Frog and pipette.

inserting the stopper, and when the solutions have completely separated, draw off the acid solution into another separator.[1] Add to the chloroform-ether mixture 10 c. c. of sulphuric acid mixture of the same strength as before, agitate well but not violently, and again draw off the acid solution into the second separator. Repeat this operation once more. Introduce into the acid solutions contained in the second separator a small piece of red litmus paper, then add ammonia water until the liquid is distinctly alkaline, and shake out with three successive portions of chloroform 15, 15, and 5 c.c.; collect the chloroform solutions in a beaker, place it on a water bath containing warm water, and allow the chloroform to evaporate completely.

To the alkaloidal residue add 3 c. c. of $n/_{10}$ sulphuric acid and 5 drops of hemotoxylin or iodeosin test-solution, then titrate the excess of acid with $n/_{50}$ potassium hydroxid. Divide the number of c. c. of $n/_{50}$ KOH used by 5 (to reduce it to $n/_{10}$), subtract the quotient from 3 (the 3 c. c. of $n/_{10}$ H_2SO_4), and multiply the remainder by 0.0287 (1 c. c. $n/_{10}=0.0287$ Gm. of atropin), and this product by 10 (to refer it to 100 Gm. of drug); the result gives the percentage of alkaloids contained in the Belladonna.

III. Physiologic Standardization.— (Demonstration.)

Drugs which do not contain alkaloids often do not lend themselves to chemic standardization. In some of these cases, the strength of the drug may be estimated by its physiologic activity. The just fatal dose is generally the most definite end-reaction. This physiologic (or pharmacologic) assay is utilized especially for drugs belonging to the Digitalis group. The method is described by Edmunds and Cushny:

Ten c. c. of tincture of digitalis are evaporated on a water bath to about half (to eliminate the alcohol) and made up to the original volume with water. Three frogs of about the same size are selected, carefully weighed, and identified by strings tied to different legs. The solution is now injected into the anterior lymph-sac (see page 795); frog 1 receiving 0.45 c. c.; frog 2, 0.3 c. c.; frog 3, 0.15 c. c. (It is better to dilute the tincture three times, so that it may be more easily measured.) At the end of one hour from the time of each injection, expose the heart of each frog. The proper end-reaction exists when the heart has just ceased beating, with the ventricle in systole, and the auricles markedly distended. If all three hearts are still beating, the experiment must be repeated with larger doses; if all the hearts have been dead for some time, smaller doses must be chosen. The standard dose corresponds to about 0.007 c. c. of (10%) tincture per gram of frog.

IV. Purity Tests.— (Optional). See page 72.

Some of the most important purity tests are illustrated by the following examples, abstracted from the U. S. P.:

1. Sodii Bromidum:

(*a*) If 1 Gm. of the salt be dissolved in 10 c. c. of water and 0.1 c. c. of $n/_{10}$ H_2SO_4 be added, no color should be produced by the subsequent addition of a drop of phenolphthalein T. S.[2] even after boiling (limit of *alkali*).

(*b*) If to 10 c. c. of the aqueous solution of the salt (1 in 20) 1 c. c. of chloroform be added, and then chlorin water which has been diluted with an equal volume of water be cautiously introduced, drop by drop, with constant agitation, the liberated bromin will dissolve in the chloroform, imparting to it a yellow to orange color, free from any violet tint (absence of *iodid*).

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[1] *If the liquid refuses to separate or emulsifies, proceed as follows:* If the solvent is lighter than water (as in the present case) add some saturated solution of sodium chloride; if the solvent is heavier than water, add more solvent, a little water, and a small amount of alcohol.

S. M., Nos. II and III; see text.

[2] T. S.= Pharmacopœial test-solution. The pharmacopœial strength of reagents are to be used throughout these tests.

(*c*) The aqueous solution of the salt (1 in 20), slightly acidulated with HCl, should not respond to the Time-Limit Test for *heavy metals* (see next number).

(*d*) If diluted H_2SO_4 be dropped upon some of the powdered salt, no yellow color should appear at once (absence of *bromate*).

(*e*) Ten c.c. of the aqueous solution of the salt (1 in 20), when acidulated with hydrochlorid acid, should not be rendered turbid by the addition of 1 c.c. of potassium sulphate T. S. (absence of *barium*).

(*f*) If 0.3 Gm. of the well-dried salt be dissolved in about 50 c.c. of water, and 2 or 3 drops of potassium chromate T. S. be added, it should require not less than 28.5 nor more than 30 c.c. of n/10 Ag NO_3 to produce a permanent red color.

2. Time-Limit Test for Heavy Metals:

The test consists in the successive addition of HCl, H_2S, and NH_4OH: no turbidity or color should develop at any time under the conditions, as compared with a control-sample of H_2S solution, treated in the same manner. The test discovers the presence of harmful quantities of Sb, As, Cd, Cu, Fe, Pb, or Zn. The details are as follows:

Ten c.c. of a solution of the substance in distilled water (1 in 20), contained in a test-tube of about 40 c.c. capacity, are acidulated with 1 c.c. of diluted HCl (unless otherwise directed), warmed to about 50° C., and an equal volume of freshly prepared hydrogen sulphid T. S. added, and the mixture allowed to stand, in the well-stoppered test-tube, in a warm place, at 35° C. for at least half an hour. At the end of this time any coloration or turbidity is carefully noted, ammonia water is added in excess, and the solution again examined for a coloration or turbidity.

Before the addition of the ammonia water, the mixture should still possess the odor of H_2S; if it does not, it should be thoroughly saturated with the gas and again set aside for half an hour.

Any change in the color of the solution which is being tested should be noted by comparison with the same volume of H_2S solution (which has been likewise acidulated), when viewed by reflected light while held against a white surface.

3. Ferri Sulphas:

(*a*) When slowly heated to 115° C., the crystals lose 38.87% of their weight.

(*b*) If 1 Gm. of the salt be dissolved in about 25 c.c. of water, containing 1 c.c. of diluted H_2SO_4, the solution heated to boiling, oxidized with HNO_3, and then mixed with a slight excess of ammonia water, the filtrate from the reddish-brown precipitate produced should be colorless, and, after acidulating with hydrochloric acid, should not respond to the Time-Limit Test for *heavy metals* (see preceding number).

(*c*) If another portion of the salt be oxidized and precipitated as directed above, the filtrate, on evaporation to dryness and ignition, should not leave any weighable residue (absence of salts of the *alkali-metals*).

(*d*) If 1 Gm. of the salt, in small fragments, be agitated during 4 or 5 minutes with 10 c.c. of alcohol, the filtrate should not redden moistened blue litmus paper (absence of *free acid*).

(*e*) If 1.38 Gm. of the salt, in uneffloresced crystals, be dissolved in about 25 c.c. of diluted H_2SO_4, not less than 49.75 c.c. of n/10

$KMnO_4$ should be required to impart to the liquid a permanent pink color (each c. c. indicating 2% of crystallized $FeSO_4$).

4. Acetphenetidinum:

(*a*) Melting point = 134° to 135° C.

(*b*) If 0.1 Gm. of the substance be boiled with 10 c. c. of water, it should yield a solution which, when cooled and filtered, should not become turbid upon the addition of bromin T. S. in slight excess (absence of *acetanilid*).

(*c*) If 0.1 Gm. of the substance be boiled for one minute with 3 c. c. of solution of NaOH (1 in 2), the solution cooled, and then agitated with 5 c. c. of a solution of chlorinated soda, there should be produced a clear yellow liquid, and not a purplish-red or brownish-red cloudy liquid or precipitate (absence of *acetanilid*).

(*d*) A mixture of 0.3 Gm. of Acetophenetidin with 1 c. c. of 90% alcohol should not acquire a red tint when diluted with 3 times its volume of water and boiled with one drop of $n/_{10}$ iodin (absence of *paraphenetidin*).

5. Chloroformum:

(*a*) Specific gravity: not below 1.476 at 25° C.

(*b*) If 10 c. c. of Chloroform be poured upon a piece of clean, odorless filter paper, laid flat upon a warmed glass plate, and the plate be rocked from side to side until the liquid is all evaporated, no foreign odor should become perceptible as the last portions disappear from the paper, and the paper should be left odorless.

(*c*) If 10 c. c. of Chloroform be well shaken with 20 c. c. of distilled water, and the liquid be allowed to separate completely, the water should be neutral to litmus paper, and should not be affected by silver nitrate T. S. (absence of chlorids), nor colored by pot. iodid T. S. (absence of *free chlorin*).

(*d*) If 40 c. c. of Chloroform be shaken with 4 c. c. of colorless, concentrated H_2SO_4 in a 50 c. c. glass stoppered cylinder during 20 minutes, and the liquids be then allowed to separate completely, so that both are transparent, the Chloroform should remain colorless, and the acid should appear colorless, or very nearly so, when seen in a stratum of not less than 15 Mm. in thickness (absence of ***impurities decomposable by sulphuric acid***).

(*e*) If 2 c. c. of the sulphuric acid, separated from the Chloroform, be diluted with 5 c. c. of distilled water, the liquid should be colorless and clear, and, while hot from the mixing, should be odorless, or give but a faint vinous or ethereal odor (absence of ***odorous decomposition products***). When further diluted with 10 c. c. of distilled water, it should remain clear, and should not be affected by silver nitrate T. S. (absence of ***chlorinated decomposition products***).

6. Æther:

(*a*) Specific Gravity: 0.716 to 0.717 at 25° C.

(*b*) Ether should boil when a test-tube, containing some broken glass and half filled with it, is held for some time closely grasped in the hand.

(*c*) The color of light blue litmus paper moistened with water should not be changed to red when the paper is immersed in Ether for 10 minutes.

(*d*) Upon evaporation, Ether should leave ***no residue***.

(*e*) As in Chloroform, (*b*).

(*f*) When 20 c. c. of Ether are shaken, in a graduated tube, with 20 c. c. of water, just previously saturated with Ether, the ether-layer, upon separation, should measure not less than 19.2 c. c. (absence of an ***undue amount of alcohol or water***).

(*g*) If 10 c. c. of Ether be shaken occasionally, during one hour, with 1 c.c. of pot. hydroxid T.S., no color should be developed in either liquid (absence of *aldehyd*).

EXERCISE 10.— SPECIFIC REACTIONS OF IMPORTANT ORGANIC DRUGS.

Study after Chapter V. Two students may work together.

The main object of this exercise is to familiarize the student with the reactions which are utilized in toxicologic analysis. It must be remembered that impure products give these tests very imperfectly. They may, however, be applied to tablets, capsules, etc., especially if these are first treated as in Exercise 9, I. The tests need not be memorized. The results should be entered in the notes. The physiologic tests should not be tried at this time. Detailed reference to them will be found in the Index. When the dry substance is used, the reaction is performed on a glass slide or watch-glass, placed on white paper; or on a porcelain slab. A piece of broken evaporating dish may be used if the reaction requires heat. A mere trace of the substance, about a milligram, should be employed. When solutions are used, the reactions are generally made in a test-tube or capsule. The student should remember that he is handling very strong poisons.

I. ALKALOIDS.

1. **Strychnin.**— To a trace of the powdered alkaloid add:

(*a*) A drop of conc. H_2SO_4: no change; then a small crystal $K_2Cr_2O_7$. Play of colors through blue, violet, red, orange (Otto).

(*b*) A drop of conc. HNO_3; heat gently: with most samples a yellow color, due to Brucin.

(*c*) Determine the dilution at which the bitter taste of strychnin just disappears (begin with 1 : 50,000; to 5 c.c. of this, add water in portions of 1 c.c.).

(Physiologic test: peculiar convulsions in frogs.)

2. **Brucin.**— (*a*) To a little of the powdered alkaloid add a small drop of nitric acid: blood-red color. Add a few drops of 1% sodium thiosulphate (hyposulphite): violet color (Cotton).

(*b*) To some powdered Nux Vomica add a drop of conc. HNO_3: orange color, due to Brucin.

3. **Caffein.**— Moisten some powdered alkaloid with nitric acid: yellow to orange color. Evaporate the excess of acid on waterbath and expose to ammonia vapor: garnet to purple color (Murexid reaction of Stenhouse, Rochleder).

4. **Morphin.**— (*a*) To a 1 : 1,000 solution add a little fresh sodium iodate solution, a few drops of dilute sulphuric acid, and a little starch-paste: blue color. This is a very delicate test, but is also given by other reducing substances (Mohr).

(*b*) To a little (2%) *aqueous* solution in a test-tube add a drop of ferric chloric: blue color (Schaer).

(*c*) To a trace of powdered alkaloid add a drop of nitric acid and heat: orange color.

(d) To a trace of dry alkaloid add a drop of fresh Marquis' (Kobert's) reagent (conc. H_2SO_4, 20 c.c.; 40% formalin, 1 c.c.). Play of colors from purple-red to violet blue.[1]

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[1] This reagent gives somewhat similar reactions with phenols and their derivatives (carbolic acid, salicylic acid, resorcin, etc.). (Optional experiments). The color in the cold is, however, more pink than with morphin, carbolic acid being the only one which could give rise to a mistake. This can be removed by boiling the acidulated solution until it ceases to give the phenol reactions (Hatcher).

S. M.— Waterbaths.

(*e*) Mix a trace of dry alkaloid with an equal quantity of ammon. molybdate, and add a drop of concentrated sulphuric acid (Froehde's reagent): violet color, changing to deep blue.

(*f*) To a few drops of (2%) aqueous solution in a test-tube add about 2 c. c. conc. HCl and a few drops of conc. H_2SO_4. Boil in water bath for one-half hour: Apomorphin is formed, see No. 7 (*b*). Neutralize with Na_2CO_3 (solution) and add a drop of alcoholic Iodin: emerald color. Shake with ether: this takes a violet color (Pellagri's reaction — also given by codein).

5. **Codein.**— Place a little of the dry alkaloid in a capsule and add a few drops of conc. H_2SO_4: faint greenish, then violet color. Add a drop of conc. HNO_3: plays from yellow to purple.

6. **Meconic Acid** (serving as a test for opium).— Dilute a few drops of tinct. opii with water and add drop of ferric chlorid: red color, not bleached by $HgCl_2$.

7. **Apomorphin.**— (*a*) To a trace of dry alkaloid add a drop of nitric acid: blood-red color.

(*b*) To a few drops of 1 : 500 watery solution (note the green color) add five drops of Na_2CO_3 and a drop of alcoholic iodin: emerald color. Shake with ether. This becomes violet.

8. **Cocain.**— (*a*) Heat a little dry cocain in a test-tube with a few drops of alcohol and of conc. H_2SO_4: fruity odor of methyl-benzoate (Biel).

(*b*) Boil 20 drops of a fresh 1% watery solution with 20 drops of 5% sulphuric acid for a few minutes; neutralize exactly with NaOH and add a drop of Fe_2Cl_6: brown precipitate of ferric benzoate.

(*c*) A mixture of cocain and calomel is blackened by moistening with dilute alcohol (Flückiger).

(Physiologic test: Local anesthesia.)

9. **Atropin.**—Place a trace of dry alkaloid in a test-tube. Add 10 drops of conc. H_2SO_4, and heat until it becomes brown; then add 2 volumes of water: characteristic odor, resembling tuberose (Gulichno), strengthened by $KMnO_4$ (Reuss).

(Physiologic test: Dilation of pupils.)

9 1-2. **Physostigmin.**— (*Optional.*)— (Notice pinkish color.) (*a*) To 1 : 1,000 aqueous solution add 1 drop of NaOH: red, becomes green on heating, and returns to red on cooling. Add Sulphurous Acid: again colorless (Eber).

(*b*) Evaporate some solution with a few drops of NH_3: red color, leaving dry blue residue. Add water: blue solution. Add Acetic Acid: violet in transmitted, coppered fluorescent in reflected light.

(Physiologic test: Constriction of pupil.)

10. **Veratrin.**— To a trace of powdered alkaloid add:

(*a*) A drop of conc. H_2SO_4: yellow color. Apply heat: the color changes through orange and deep scarlet to a beautiful violet red.

(*b*) A drop of conc. HCl and heat: red color (Trapp).

(Physiologic test: Peculiar action on muscle.)

11. **Quinin.**— Use a saturated aqueous solution of quinin sulphate.

(*a*) Notice the blue fluorescence, best seen by drawing the solution into a pipette. This is increased by acids, diminished by NaCl.

(*b*) Thalleioquin Reaction: Add 2 drops of Bromin Water and then cautiously an excess of ammonia. An emerald color results, which is changed to red by HCl. (If a very small quantity of ammonia is used, the color may be magenta.) (Brandes, André.)

12. **Epinephrin.**— To some 1 : 50,000 solution of adrenalin, or to a dilute extract of suprarenal gland, add some ferric chlorid, drop by drop, as long as the color darkens: a green color develops. Add some NaOH: the color changes to a dark brownish-red (Vulpian's Chromo-

gen Reaction). Dilute solutions of epinephrin turn pink on prolonged standing.

(Physiologic test: Rise of blood pressure.)

(The following alkaloids are identified especially by physiologic tests:
Aconitin: prickly taste, action on frog's heart.
Coniin, Nicotin: odor, paralysis of ganglia, of motor endings.
Curare: paralysis of motor endings.
Pilocarpin: salivation.)

II. GLUCOSIDS AND NEUTRAL PRINCIPLES.

13. Digitalin.— Use a trace of the dry substance:

(*a*) Add a drop of Fe_2Cl_6, and of conc. H_2SO_4, *without mixing:* carmin to violet zone, changing to indigo (Kiliani).

(*b*) Dissolve in glacial acetic acid in test-tube. With a glass rod, add the merest trace of Fe_2Cl_6. Add equal volume of conc. H_2SO_4 *without mixing:* persistent carmin zone (Keller).

(*Digitoxin* also gives a characteristic reaction with (*b*), the zone changing from dirty brown to blue-green and indigo.)

(Physiologic test: Slowing and systolic standstill of frog's heart.)

14. Santonin.—

(*a*) Dissolve a little in alcohol, add a small piece of dry KOH, and warm: reddish-green to yellow color (Banfi).

(*b*) To a trace of the dry substance add a little concentrated sulphuric acid, and a drop of ferric chlorid, and heat: dark red color, changing to violet brown.

(*c*) Santonin in urine: Consult Exercise 13.

14 1-2. Picrotoxin.—(*a*) Note the intensely bitter taste (one! drop of 1 : 1,000 solution on tongue).

(*b*) Mix an equal quantity (trace) of picrotoxin and powdered potassium nitrate; add a drop of concentrated sulphuric acid, and then, drop by drop, a strong sodium hydrate solution: brick-red color (Langley's Reaction).

(Physiologic test: Peculiar convulsions of frog.)

III. COAL-TAR DERIVATIVES.

15. Carbolic Acid.— Use 3 : 1,000 solution.

(*a*) Add Fe_2Cl_6: blue-violet color.

(*b*) Add bromin water: yellow precipitate of needle-shaped crystal (Landolt).

(*c*) Add Millon's reagent and heat: blood-red color or precipitate (Plugge).

(*d*) Note that the reaction of strong carbolic acid to litmus paper is neutral.

16. Resorcin.—To a trace add some NaOH and $CHCl_3$: Pink color (Reuter).

17. Acetanilid.— (*a*) Heat some of the powder with NaOH solution: Dissolves, with odor of anilin; add a few drops $CHCl_3$ and heat again: Odor of phenyl-isonitril (resembles witch-hazel). [This reaction is also given by anilin (see first edition, page 769); by phenacetin, etc.] (Hofmann.)

(*b*) Boil with conc. HCl, add equal volume 5% C_6H_6O and equal volume calx chlorata: Red turbid fluid. Supersaturate with NH_3: Deep blue. (Berthelot, Vulpius.)

(*c*) Rub together equal volumes of Acetanilid and $NaNO_2$ and add some conc. H_2SO_4: Orange liquid.

18. Phenacetin.—Gives (*a*) and (*b*), as in 17. These need not be repeated. With (*c*) gives a black violet color, later passing into green.

19. Antipyrin.—(*a*) To an aqueous solution add a few drops conc. Fe_2Cl_6: Deep red solution: + H_2SO_4: Light yellow (Cohn, Knorr).

(*b*) To an aqueous solution add some Spiritus Ætheris Nitrosi. Slow development of green color and precipitate of isonitroso-antipyrin.

20. Salol.—(*a*) Alcoholic solution + Fe_2Cl_6: Red-violet color.

(*b*) Dry crystals + NaOH; heat: Dissolves. Add conc. HCl: Crystalline precipitate of salicylic acid and odor of phenol.

IV. ORGANIC ACIDS.

21. Salicylic Acid.—Use Sodium Salicylate.

(*a*) To a dilute solution add a drop of ferric chlorid: Red-violet color.

(*b*) Place some dry salicylate in test-tube; add equal parts of methyl alcohol and conc. H_2SO_4 and heat: odor of methyl salicylate (oil of wintergreen).

22. Benzoic Acid.—To dilute solution of sodium benzoate add drop of ferric chlorid: brownish-pink precipitate. Add a little dilute HCl: dissolves. (A white precipitate of benzoic acid may be thrown down, if the solution was concentrated.)

23. Acetic Acid.—Use sodium acetate.

(*a*) To a dilute solution add drop of ferric chlorid: red color.

(*b*) Heat some dry acetate in a test-tube with equal volumes of alcohol and conc. H_2SO_4: odor of ethyl acetate (acetic ether).

24. Hydrocyanic Acid.—(*a*) Notice odor.

(*b*) Impregnate some filter paper with freshly prepared Tincture Guaiac, let dry, then pour on some very diluted $CuSO_4$; expose this to the vapor of 1 : 1,000 HCN: Deep blue color (Pagenstecher, Schönbein, Preyer). Expose another paper prepared in a similar manner to the vapor of NH_3: Green color.

(*c*) Add to 1 : 1,000 solution some $FeSO_4$ and Fe_2Cl_6 and a few drops of NaOH; boil, let stand a few minutes, acidulate with conc. HCl, and heat: Green to blue color, or precipitate of Berlin blue (Husemann, Ittner).

25. Oxalates.—To a solution of potassium oxalate add $CaCl_2$: Precipitate. Add acetic acid: does not dissolve. Add dilute HCl: solution.

V. HYDROCARBONS.

26. Alcohol.—(Use 5% solution.)

(*a*) Add some $K_2Cr_2O_7$ and dilute H_2SO_4 and warm: Green color and odor of aldehyd or acetic acid.

(*b*) Add some NaOH and Iodin solution; heat gently: Odor of iodoform; and precipitate of this substance may be seen; examine with microscope (Lieben).

(*c*)[1] Place a pint of beer in a liter flask. Stopper tightly with a perforated cork bearing an upright glass-tube of a bore of 1/6 inch and at least 4 feet high. Heat slowly to boiling, and continue the heat until the foaming subsides. Apply a lighted match to the upper end of the tube: The alcohol vapor will ignite, most of the watery vapor being condensed in the long tube.

26 1-2. Methyl Alcohol (Wood-Alcohol).—(*a*) The test 21 (*b*) may be modified to apply to methyl alcohol.

(*b*) *Test for the presence of wood-alcohol in grain alcohol:*[1] Apply the following tests to two solutions, one containing 10% of ethyl alco-

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S. M. Demonstration of 26 c and 26 1-2 b; plain and formaldehyd milk.

[1] Demonstration.

hol, the other 5% of methyl and 5% of ethyl alcohol. Determine which sample is adulterated. Place 10 c.c. of the solution in a large test-tube. Heat a spiral of copper-wire red hot and plunge into the solution. Repeat this five or six times. (This converts methyl alcohol into formaldehyd; the further test is for this substance.) Filter. Boil very gently until the odor of acetaldehyd disappears. Pour into a test-tube and cool. Add one drop of ½% resorcin solution; shake. Pour a portion of this liquid into a second test-tube, containing concentrated sulphuric acid, held in an inclined position, so that the two liquids do not mix. Let stand three minutes and rotate slowly: A rose-red ring indicates methyl alcohol (due to formation of formaldehyd).

27. **Chloroform.**— Add some NaOH and a trace of resorcin: Pink color (Crismer, Schwarz).

28. **Chloral.**— (*a*) As 27: gives same result.

(*b*) Dissolve in water and add NaOH: odor of chloroform.

29. **Formaldehyd.**— Use two samples of milk, one pure, the other mixed with 1 : 5,000 absolute formaldehyd.

(*a*) *Hehner's Test:* To about an inch of conc. H_2SO_4 in test-tube add few drops of Fe_2Cl_6 and mix; pour on formalin milk without mixing: Violet zone. In applying this test to pure formaldehyd solution, 1 c.c. of pure milk or of peptone solution must be added to 5 c.c. of the formaldehyd solution.

(*b*) *Liebermann's Test:* Mix some of the formalin solution with a drop of 5% Phenol solution and pour cautiously, without mixing, on some conc. H_2SO_4 in test-tube: Crimson zone.

VI. PRELIMINARY TEST FOR INORGANIC POISONS.

30. **Reinsch's Test.**— Boil a slip of thin bright copper foil (about 1 c.m. square) in a test-tube with 10 c.c. of concentrated HCl: If the reagents are pure, it remains bright. Add some of the suspected liquid (say a solution of arsenic) and boil again for half an hour: a dark stain may denote As, Sb, Hg, Bi; no stain proves the absence of these metals.

31. **Preliminary Test for Phosphorus.**— Place some phosphorus water in a small bottle; stopper it loosely and between the cork and the neck of the bottle suspend two pieces of filter paper, the one impregnated with Silver Nitrate, the other with Lead Acetate. If the silver paper is blackened and the lead paper not, the presence of Phosphorus is rendered probable. (If both are blackened, this indicates H_2S.)

(The apparatus for distillation with steam, the Mitscherlich and the Marsh apparatus, may be shown in operation.)

32. **Inorganic and Organic Iron.**— The medicinal iron preparations are either salts of iron, or the iron is a firmly bound constituent of the molecule. The first class (inorganic irons) give the ordinary iron reaction; the latter (organic or masked iron) do not.

(*a*) *Macallum's Reaction:* This is the most delicate: a drop of fresh ½ hematoxylin solution gives a blue-black color with inorganic iron but not with organic. The test is best applied to the dry substance or concentrated solution. Confirm that the following preparations are correctly classed:

Inorganic:		Organic:	
	Ferric sulphate.		Dried blood.
	Scale salt of iron.		Egg yolk.
	Iron albuminate.		Iron Somatose.

S. M.— Steam-retort, Mitscherlich and Marsh apparatus.
S. M.— No. 32.

(*b*) The action of dilute hydrochloric acid liberates the inorganic iron from some of the masked compounds, but not from others. To demonstrate this, add a little 5% hydrochloric acid and a drop of potassium ferrocyanid to ovoferrin and to egg-yolk, and boil: The first gives the Prussian blue reaction, the second not.

Lay some alcohol hardened sections of spleen in the ferrocyanid, and others in the acid-ferrocyanid mixture. Spleen contains loosely bound organic iron (ferratin) and therefore colors in the acid mixture, but not in the plain ferrocyanid.

33. Sweetening Agents.— Determine the sweetening power of Lactose, Glucose, Levulose, Glycerin, and Saccharin, as compared with 1% Cane Sugar. Start with a 10% solution of the first four, and a 0.01% solution of saccharin. (The experiment may be divided between several students.) Dilute the solution to be compared with an equal quantity of water, and continue until it tastes less sweet than the cane sugar. Then try two dilutions between this and the preceding. Note that the taste differs somewhat qualitatively. Tabulate the conclusions as multiples of cane sugar (*f. i.*, saccharin = 300 × cane).

SUPPLEMENT TO EXERCISE 10.

The preceding exercise should be supplemented by the examination of unknown substances; the use of text-books being permitted. For instance:

Do the substances or solutions submitted to you contain:[1]	1, *a* and *b*:	Nitrogen?
	2, *a* and *b*:	An alkaloid?
	3, *a*, *b*, and *c*:	Caffein or morphin?
	4, *a*, *b*, and *c*:	Opium?
	5, *a*, *b*, and *c*:	Veratrin or quinin?
	6, *a*, *b*, and *c*:	Salicylic, hydrocyanic, or carbolic acid?
	7, *a*, *b*, and *c*:	An oxalate or acetate?
	8, *a*, *b*, and *c*:	Phenacetin, salol, or acetanilid?

EXERCISE 11.— DETECTION OF PRESERVATIVES IN MILK.

Study after Chapter V or XVII.

A pure and an adulterated sample should be submitted for each test, the student being required to detect which is adulterated. The following proportions may be used, per liter of milk: *Formaldehyd*, 0.1 c. c. of formalin; *salicylic acid*, 0.2 Gm.; *benzoic acid*, 0.5 Gm.; borax, 1.5 Gm. The preliminary distillation, evaporation and incineration may be performed by members of the class, or by the demonstrator; the products being examined by students in pairs.

1. Formaldehyd.— As a preliminary, apply Hehner's test (29 *a*, Ex. 10) directly to the milk; then distill 100 c. c. of the milk, collecting the first 10 c. c. of the distillate. Mix 5 c. c. of distillate with 1 c. c. of pure milk, and apply Hehner's test (Exercise 10, No. 29).

2. Salicylic and Benzoic Acid.— Evaporate 50 c. c. to dryness on water bath; extract with alcohol acidulated with HCl; neutralize the filtered extract with ammonia; evaporate to small bulk and extract with water. Test by Ex. 10, No. 21 (*a*) and 22 (*a*).

3. Borax or Boric Acid.—Evaporate 20 c. c. to dryness; incinerate with $NaHO_3$; dissolve in HCl; moisten strip of turmeric paper with this solution; dry at 100° C.: red color, changed to black by sodium hydrate.

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[1] No solution contains more than one substance.

S. M.— No. 32.

S. M.— Unknown solutions.

S. M.— Pure and preserved milk, etc.— See exercise 11.

EXERCISE 12.—TOXICOLOGIC ANALYSIS (*Optional*).

Some mixtures containing unknown poisons may be submitted to students for systematic analysis, if the time permits, or as electives. See Chapter V; and Schaer and Zenetti (page 791).

It is better to let the beginner know to which analytic group the poison belongs. The following may be suggested:

Free Acid and Alkali.

Volatile Poisons.— Phenol, HCN, Turpentine, Phosphorus (also with admixture of alcohol), Chloroform, Chloral, Formaldehyd, Nitrobenzol.

Fixed Organic Poisons.— Acetanilid, Morphin (also in presence of quinin and caffein); Aconite, Digitalis, Strychnin (also in presence of Aloes), Oxalic Acid, Atropin, Picrotoxin.

Metals.— As, Sb, Hg (also in presence of Bi), Pb. Quantitative estimation of As. Arsenic in wall-paper. Excess of lead in solder. Excess of copper in preserved peas.

EXERCISE 13.—TESTING FOR DRUGS IN THE URINE.

Study in connection with Chapter V or VII.

The drugs mentioned in the text may be distributed amongst the students. The urines should be collected for 24 hours, the time of collection of each sample being noted. The samples are to be distributed so that each student need analyze but one specimen for each drug. A reporter should be appointed, who will collect and tabulate the results of the entire class, and render a report at the next meeting.

The notes should indicate when the excretion of each drug is first observed, when it reaches its maximum, and whether it disappears again during the period of collection. These data will be gathered from the class-report.

Explanatory.— Many drugs are excreted by the urine; some unchanged, such as quinin, iodid, etc.; others after having undergone partial decomposition or other chemic changes during their sojourn in the body (acetanilid, salol, chrysophanic acid, santonin, etc.). The original drug or its derivative may then be demonstrated in the urine. This may be important in toxicology, or to the physician who may be interested in seeing whether the patient is following his directions. These reactions (particularly the salol, methylen blue, and iodid), are also utilized to study the rapidity of absorption and excretion in pathologic conditions. Many drugs are so altered in the body that they cannot be found in the urine.

Experiments:

1. Indophenol Reaction.— (Given by *Acetanilid*, *Phenacetin*, and other phenetidin derivatives):

Use urine after taking 0.3 Gms. of Acetanilid. To about 10 c. c. of urine add ¼ volume of concentrated HCl; boil; allow to cool; add ⅙ volume of 5% carbolic acid, and a few drops of pot. bichromate solution; red color; add ammonia: blue color. (The acetanilid is excreted as a paramidophenol compound with glycucuronic and ethyl-sulphuric acid; the paramidophenol is liberated by the HCl, and gives the above color reaction.)

2. Salol.— Urine after taking 0.3 Gms. of Salol:

Acidulate a little of the urine in a test-tube with strong sulphuric acid; add an equal volume of ether, shake, draw off the ether with a pipette into another test-tube, add to it an equal volume of water, and a drop of ferric chlorid; shake: violet color.

3. **Chrysophanic Acid.**— (Appears in the urine after taking senna, rhubarb, cascara sagrada, etc.) Use urine after taking 2 c. c. of Fluidext. Rhei.

The urine is reddish brown. Add some NaOH: deep red color.

4. **Santonin.**— Urine after 0.03 Gm. Santonin.

The urine has a lemon yellow color. Add NaOH; pink or red. The (unknown) coloring matter is not precipitated by lime water (difference from chrysophanic acid, Munk, 1878). If it is shaken with ether, it passes into this solvent.

5. **Alkaloids (Quinin).**— Urine after 0.2 Gm. Quinin.

Acidulate with dilute sulphuric acid and add drop of merc. pot. iodid; precipitate.

6. **Copaiba.**— (Urine after 10 Gm.)

(*a*) Add conc. HCl: red color, becoming violet on heating. The spectroscope shows bands in the blue, green, and orange. (Quincke, 1883). The reaction is not produced by all samples of the drug.

(*b*) Add ammonia: light brown or bluish fluorescence.

(*c*) Boil: precipitates; add alcohol; dissolves.

(*d*) Test for sugar: the result is often positive (due to glycuronic acid).

7. **Methylen Blue.**— (Urine after 0.1 Gm.)

The urine has a blue or green color, after 30 to 50 minutes. (Decolorizing under the action of bacteria.)

(*a*) Boil with a few drops of conc. HCl: the color becomes pinkish red; neutralize with NaOH: returns to green.

(*b*) Add a few drops of NaOH, boil and add a few drops of 1% glucose[1] solution: the color disappears, but reappears on shaking.

8. **Iodid.**— (Urine after 0.3 Gms. of potassium iodid.)

Add a few drops of dilute sulphuric acid, a little 10% $NaNO_2$, and some 2% starch paste; bluish color.

9. **Antipyrin.**—(Urine after 0.3 Gm.) Add a few drops of Fe_2Cl_6: reddish-brown color.

10. **Methyl salicylate.**— Rub 2 c. c. of oil of wintergreen into the skin. Test the urine as for salol. (This also illustrates absorption from the skin.)

11. **Sodium Acetate or Citrate.**— Empty the bladder and note that the reaction of the urine is acid to litmus. Take 10 Gm. of the salt, dissolved in water. The reaction of the urine will be found alkaline after a few hours, the organic salt being oxidized to carbonate in the body.

EXERCISE 14.— CHEMIC ANTIDOTES.

Study in connection with Chapter V, p. 88. Consult Exercises 18 C and 29 for the application of antidotes to animals.

Explanatory.— One of the first objects in treating a case of poisoning is to render the poison insoluble, thereby delaying its absorption. The agent which is used for this purpose must itself be almost harmless, so that it can be given in unlimited quantity. With this restriction, any precipitant may be used. (It is useful to remember that these precipitants are generally employed as tests for the substance.) The subject is also simplified by the fact that the same chemic antidotes are used for all alkaloids.

Notes.— State your observations; explain the chemic changes.

Conclusions.— Tabulate the chemic antidotes for alkaloids, metals, lead, barium, oxalates, phosphorus.

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[1] The urine often contains enough reducing substance to decolorize on heating, even without the addition of glucose. This may be tried.

Experiments:

1. *Alkaloids and Tannin.*—(*a*) To some $^1/_{10}$% solution of Strychnin Sulphate add a little infusion of tea: large precipitate: Add to half of this some alcohol, to the other half some dilute HCl: The precipitates dissolve.

(*b*) Repeat with $^1/_{10}$% Morphin Sulphate: only a slight precipitate.

(*c*) Repeat (*a*) with coffee infusion: only a slight precipitate.

Tannin is an efficient precipitant of some alkaloids, but not of others (see page 89). Coffee is less efficient than tea. The precipitates dissolve in alcohol and in dilute acids.

2. *Alkaloids and Iodin.*—To some saturated aqueous Quinin Sulphate add some solution of iodin in KI: large precipitate. Add some alcohol: the precipitate dissolves.

3. *Alkaloids and Permanganate.*—To some quinin solution add solution of $KMnO_4$; brown precipitate. Add alcohol: no solution.

The reactions 2 and 3 apply to all alkaloids, so that these reagents may be considered universal alkaloidal antidotes.

4. *Metals and Tannin.*—(*a*) Add some tea to Lead Acetate: large precipitate. Add to half of this some alcohol: no solution; to the other add dilute HCl: The tannate is decomposed and lead chlorid is precipitated.

(*b*) Repeat (*a*) with $HgCl_2$: very little precipitate.

(*c*) Repeat (*a*) and (*b*) with coffee: results similar to tea.

Some metals are precipitated by tannin, others not. The precipitates are insoluble in alcohol, somewhat soluble in dilute acids.

Coffee-tannin is also effective, but less than tea.

5. *Metals and Proteids.*—Mix some $HgCl_2$ and albumin solutions: large precipitate: Practically all metals are precipitated by proteids.

6. *Barium and Sulphates.*—To some barium chlorid solution add Na_2SO_4 solution: white precipitate.

7. *Oxalates and Calcium.*—To a solution of potassium oxalate add some $Ca(OH)_2$: precipitate.

8. *Phosphorus and Copper.*—Drop a small piece of phosphorus into a dilute solution of $CuSO_4$: The phosphorus is soon covered with a film of metallic copper.

EXERCISE 15.—CHEMIC CORROSIVES.—ACTION ON PROTEIDS AND BLOOD.

Study in connection with Chapter XXVIII. Also consult plates in Von Hofmann's Atlas of Legal Medicine.

Explanatory.—All substances, which enter directly into chemic combinations with proteids, produce local effects, *i. e.*, they act at the place where they are applied. The action results in inflammation; these substances are therefore *irritants;* if the action is at all violent, the cells are killed. If the combination of the reagent and protoplasm is fluid, the tissue is dissolved. This is termed *corrosion or cauterization.* If, on the other hand, the action is mild, and the product insoluble, the effect is *astringent; i. e.*, mucous membranes are constricted and puckered, and the phenomena of a pre-existing inflammation are lessened. These precipitates also serve to stop the lumen of bleeding vessels, and are therefore *styptic* or *hemostatic.*

It is therefore important to know whether the action of these agents results in precipitation or solution. This may be studied on isolated proteids. It must be remembered, however, that the effects depend greatly upon the concentration of the reagent: the precipitates often re-dissolve in an excess of the reagent or of the proteid.

The *color* of the compounds is often important in diagnosis.

Notes.— State the results (color, precipitation, solution): state whether the addition of more reagent modifies these results.

Conclusions.— Tabulate the results to show the reagents which precipitate, those which dissolve, and those which first precipitate and then dissolve.

Which of these drugs could be applied as hemostatics?

Which give characteristic color changes?

Exercises:

I. On Proteids (Egg Albumen).— Place in each of twelve test-tubes half an inch of a solution of egg-albumen. (The white of 2 eggs to 200 c. c. of water, strained.) Add the following reagents (the usual solutions), drop by drop:

(1) $HgCl_2$; (2) $AgNO_3$; (3) $CuSO_4$; (4) Fe_2Cl_6 (tincture); (5) Lead acetate; (6) H_2SO_4; (7) HCl; (8) HNO_3; (9) NaOH; (10) Carbolic acid (strong); (11) Alcohol; (12) Tannin [6, 7, 8, 10, and 11: full strength].

A white precipitate is given by $HgCl_2$ $AgNO_3$, $Pb(C_2H_3O_2)_2$, H_2SO_4, HCl, C_6H_6O, C_2H_6O, and tannin; a greenish-white precipitate by $CuSO_4$; a yellowish-brown precipitate by Fe_2Cl_6; yellow precipitate by HNO_3. NaOH gives no precipitate.

Excess of the reagent redissolves the precipitate in the case of acids, but not with the other precipitants. (The reagents which redissolve the precipitate are apt to penetrate more deeply into tissues.)

II. On Defibrinated Blood.— Place about 2 c. c. of defibrinated blood into 12 test-tubes, and add the reagents as in I.

A black or brown clot is formed with Fe_2Cl_6, H_2SO_4, and HNO_3; a brown or dark precipitate with $CuSO_4$, HCl, and NaOH; a pink or light red precipitate with C_6H_6O, C_2H_6O, and tannin; a gray precipitate with $HgCl_2$ and $AgNO_3$. Excess of the reagent redissolves the precipitate with a brownish-red color in the case of acids, and with a garnet color in the case of soda. The others do not redissolve. (The color is due to acid hematin in the case of acid, to alkali hematin in the case of NaOH.)

EXERCISE 16.—CHEMIC CORROSIVES, CONTINUED.—ACTION ON EXCISED TISSUES.

Explanatory.— These experiments are a further application of the preceding exercise. It will be seen that the effect depends somewhat on the situation; the skin is generally more resistant. The character of the stain can be studied more satisfactorily; also the rapidity of penetration.

Notes.— Record the results.

Conclusions.— Tabulate your results to show which agents produce hardening, which softening; which characteristic stains; which act deeply and which superficially. Which are the most powerful depilatories (*i. e.*, removing hair).

I. Corrosion of Skin.—Place bits of fresh mammalian skin into test-tubes containing concentrated H_2SO_4, HCl, HNO_3, NaOH, and C_6H_6O. Leave for 15 minutes, rinse in water, and note the effect on the hair, and on the epithelial and connective-tissue surfaces.

With the acids, the *epithelial surface* becomes first white, hard, and somewhat shrunken. With more prolonged action it is gradually softened. With HCl it remains white; HNO_3, light yellow; H_2SO_4, brownish. C_6H_6O causes a more pronounced shrinking, puckering, and hardening, without subsequent softening. NaOH softens. The *hair* is softened and dissolved by the NaOH, more slowly by the acids. It is not affected by C_6H_6O. The *connective-tissue* is rendered softer and transparent and is finally dissolved by the NaOH and the acids, and stained as the epithelium. The carbolic acid affects it as it does the epithelium.

II. Corrosion of Mucous Membranes.— Slit open a piece of fresh dog's intestine, 3 inches long, and flatten it, epithelial surface up. With a glass-rod apply a drop of the reagents used in I. Observe during 15 minutes. Note the character, color, and depth of the effect. See whether the epithelium detaches more readily. The acids first turn the epithelium white and hard, but soon softer and darker. The underlying tissues appear white and hard, as if cooked. The epithelium is readily detached. The action extends deepest with HNO_3. This gives a yellow tinge to the stain. H_2SO_4 gives a brownish color. C_6H_6O acts as it does on the skin; its effect extends deeply. NaOH first softens the tissues, and then renders them gelatinous. The epithelium scrapes off very readily.

III. Corrosion of Muscle.— Place bits of muscle into the reagents used in I, and observe during 15 minutes. Rinse in water and note appearance and consistency.

H_2SO_4 and HCl soften the muscle, without swelling it; the color becomes a deeper red; the muscle then gradually disintegrates, dissolving entirely, with a garnet color, in the case of the H_2SO_4. In HNO_3 the muscle shrinks and hardens, the color changing to yellow or brown, with partial solution. In C_6H_6O, the muscle is bleached, shrinks, and becomes hard, assuming a "cooked" appearance. NaOH causes the muscle to become red and swollen; the outer layers soften, become gelatinous, and dissolve to a red solution.

IV. Coagulation of Muscle.— Trace a bit of fresh frog's muscle in normal saline on a slide, examine with the lower power of the microscope: add a drop of concentrated H_2SO_4 and observe the results. Repeat with the other reagents mentioned in I, and also with 1% caffein.

The acids cause the fibers to shrivel and to become contorted; they turn granular and opaque, the striations are lost, and gradual solution occurs. C_6H_6O acts at first like the acids, but there is no solution. NaOH causes the fibers to swell, to become transparent, and to gradually dissolve. Caffein produces a granular opacity.

EXERCISE 17.— CHEMIC CORROSIVES, CONTINUED.— STAINS ON HUMAN SKIN.

Explanatory.— It will be seen that the observations made on excised tissues apply also to the human skin. The stains may be removed in the manner indicated in the experiment.

Check the results.

Exercises.— 1. Apply to the intact skin of the forearm a drop of *concentrated nitric acid*. Wash off as soon as there is itching. An intensely yellow stain develops. Apply a drop of ammonia, the stain turns to an orange brown (xanthoproteic reaction). It is very lasting and wears off only as the skin is desquamated.

2. Apply to another place a drop of saturated *picric acid;* yellow stain. Apply ammonia; the stain is removed.

3. Apply concentrated *sulphuric acid* and *hydrochloric acid* to different places; wash off as in 1; there is no stain, but redness.

4. Apply strong alcoholic solution of *methylen blue;* wash off after one hour. The stain is not removed by water, but by rubbing with dilute ammonia.

5. Apply a drop of tincture of *iodin*, leave for five minutes: ma-

S. M.— Dead dog; scissors and forceps; frog; microscope.

hogany stain which cannot be washed off. Apply ammonia, the stain is removed (formation of soluble NH_4I).

6. Apply a drop of 10% $AgNO_3$ solution and leave it; a black stain develops quite slowly. It cannot be removed by water. Apply a drop of tincture of iodin and then ammonia; the stain disappears (AgI is formed and this is soluble in ammonia).

7. Apply $AgNO_3$ as in 6 (being careful that the skin is not abraded); rinse the stain with some dilute solution of KCN; it disappears (formation of the soluble double cyanid).

8. *Carbolic Acid.*— Consult the next exercise.

EXERCISE 18.— PHYSIOLOGIC EFFECTS OF IRRITANTS.

Study in connection with Chapter XXVIII.

Explanatory.— The tissues respond to irritants by the phenomena of inflammation. Four successive stages may be recognized *in the skin:* (1) *Rubefaction,* or reddening with pain and itching; (2) *Vesication,* or blistering; (3) *Pustulation,* the formation of isolated pustules; and (4) *Corrosion,* or destruction of tissue. The degree of the action depends on the nature and the concentration of the irritant. The rapidity of action is also variable. Chloroform and turpentine, for instance, act quickly, but scarcely progress beyond rubefaction; cantharides, croton oil, and antimony act slowly, but progress, the first to vesication, the last two to pustulation. A quick action is generally associated with volatility. Vesication demands that the irritant should remain in the skin sufficiently long to produce an inflammatory exudate under the impermeable stratum corneum. Pustulants have a specific chemotactic power on leucocytes.

Mucous membranes show only rubefaction and corrosion; the anatomic conditions being unsuitable for vesication or pustulation. The mouth, however, is an exception, for vesication may occur here. Irritation of mucous membranes is also characterized by catarrh — *i. e.,* increased excretion of mucus. This is diminished by *astringents.* These also cause puckering.

Irritation of the lower portions of the alimentary canal is studied in Exercise 32.

The *treatment of irritation* consists in the removal of the irritant and the application of fats, glycerin, or mucilage. This may be studied on carbolic acid.

Record your observations. Draw the conclusions.

The exercises marked * are optional.

Exercises.— A. Irritants on the Skin.— 1. Rubefaction.— Rub a little chloroform on the arm. Note the burning and reddening.
form on the arm. Note the burning and reddening.

*** 2. Vesication.**— Apply some cerate of *cantharides;* vesication after some hours. (Wash off the excess of the cerate with alcohol.)

*** 3. Pustulation.**— (*a*) Apply a drop of a 25% solution of croton oil in cottonseed oil to the skin of the arm; a pustular eruption is developed after some time.

(*b*) Apply some 10% ointment of *tartar emetic;* pustular eruption. (The tartar emetic is decomposed and rendered irritant by the acid secretions of the cutaneous glands, and the pustulation remains therefore confined to these).

B. Irritants on Mucous Membranes.— * 4. Snuff a very little mixture of one part of *veratrin* and 500 parts of starch. Sneezing, and all the phenomena of acute coryza.

5. Shake a bottle containing *soap-bark* and smell it. Sneezing.

6. Place a drop of ten times diluted tincture of *aconite* on the tip of the tongue; persistent tingling sensation.

7. Place a drop of Tr. *Iodin* on inner surface of lip: blister.

8. Observe the *astringent taste* of a 5% solution of *alum*, or of Tr. Ferri Chlor.

C. Treatment of Irritation (Carbolic Acid).—9. Arrange 5 small beakers in a circle so that the fingers can be plunged into them simultaneously. Fill these beakers with 5% carbolic acid in (*a*) water; (*b*) 25% alcohol; (*c*) 25% glycerin; (*d*) turpentine; (*e*) cottonseed oil.

Insert the five fingers of the left hand, one in each solution; keep in for five minutes, withdraw and note the blanching and wrinkling, the tingling (felt especially on pressing the fingers against a table), and the anesthesia.

The effects (especially the blanching) are greatest in the water; much less in the alcohol and glycerin; practically absent in the oil.

Rinse the finger which has been in the watery solution in a liberal quantity of water: the blanching persists. Rinse it in 95% alcohol: the blanching disappears.

10. Pour a half-inch of undiluted egg-white into two test-tubes; pour over this (without mixing), in (*a*) an equal volume of 5% phenol in water; to (*b*) in oil. (*a*) precipitates at once, (*b*) very slowly. The phenol, being very soluble in oil, does not pass into the watery egg-white.

Explanatory.—The reagents (*b*) to (*e*) of Exp. 9 are all better solvents for carbolic acid than is the skin; they consequently lessen the penetration of the phenol and hence its effects (Exp. 10). (These solutions of phenol are therefore also much less efficient as antiseptics than are watery solutions.) The glycerin and cottonseed oil act in addition in virtue of their viscidity (*i. e.*, as *emollients*), hindering the access of new layers of the solution to the skin. This makes them more effective in the treatment of carbolic burns; but, on the other hand, it hinders the washing off of the phenol. Lavage of the stomach with 10% alcohol is the best local treatment in internal carbolic acid poisoning. For burns on the skin, the surface should be rinsed with the dilute alcohol and then dressed with glycerin or oil. This treatment does not lessen the effects of the carbolic acid which has been already absorbed (except that still present in the superficial layers). The systemic effects of phenol are best treated with intravenous injection of sodium sulphate. (Consult Exercise 59, No. 5 and 6.)

*11 (Optional). Dip the tips of two fingers into undiluted liquified carbolic acid for one minute. Very little burning is felt, but the skin becomes white. Now rinse the one finger in water, the other in 25% alcohol. The latter removes the blanching but not the sensory phenomena. It is effective against the superficial actions, but not against those which are situated more deeply. Glycerin, oil, or turpentine act like alcohol. Rinse the other finger in the alcohol. There will be some subsequent roughening and chapping of the skin.

EXERCISE 19.—EFFECT. OF DRUGS ON FERMENTS.

Study in connection with Chapters VII and XVII.

Explanatory.—Many chemic changes within the living organism are brought about by the aid of ferments or catalysators; *i. e.*, substances which greatly hasten specific reactions without being themselves permanently changed. Small quantities of the ferment are therefore effective. The coagulation of milk or blood; the solution and hydrolysis of proteids and carbohydrates in digestion; the phenomena of

S. M.—Experiments 9 and 10.

oxidation, etc., are examples of these actions. The ferments may act within the cells (yeast), or they may be secreted (gastric juice, etc.). Organic ferments are accelerated by moderate and destroyed by excessive heat; they are injured by a number of poisons, notably by the antiseptics, cyanids, and quinin. With the last two, the activity reappears when the poison is removed. Most ferments require a certain reaction of the medium, neutrality, or a specific degree of acidity or alkalinity. Certain ferments, especially rennin and fibrin-ferment, also require the presence of calcium, which probably participates in the reaction.

Finely divided inorganic matter — such as spongy platinum and other metals in "colloidal solution"— also act as ferments; probably by "surface action"; *i. e.,* by condensing molecules on their extensive surface and thus bringing them in closer contact. It is remarkable that these inorganic ferments are impeded by the same poisons as the organic, and in correspondingly small quantities. This does not suffice to establish the identity of the mechanism of action of the two classes of ferments. With the inorganic ferments, the retardation is doubtless due to alteration of the surface produced by chemic actions.

The effects of ferments are generally studied in physiology. A mere reference to them suffices. The comparison of the retarding effects of poisons requires so many precautions that the results are apt to be unsatisfactory in an elementary course. The experiments are therefore made *optional.*

Experiments.— (See Stewart's Manual or Practical Physiology, Beddard, etc., for the details of these experiments.)

A. Physiology of Ferments.— 1. Peptic Digestion.— Demonstrate the solution of fibrin; the production of albumoses and peptones; the influence of reaction and temperature.

2. Papain Digestion.— As above. Papain is a vegetable ferment: its action is largely independent of the reaction of the medium.

3. Pancreatic Digestion.— As above. Also show the accelerating action of enterokinase (the scrapings from the duodenal mucosa), which converts the inactive trypsinogen into active trypsin. Also study the amylolytic and lipolytic ferments of the pancreas.

4. Coagulation of Milk.— Study the effect of rennin; the effect of temperature (about 40° C. is the optimum). Confirm that the coagulation does not occur when the calcium is removed by excess of an oxalate, but reappears when an excess of calcium chlorid is added. The effect of the addition of barley water and formaldehyd may be demonstrated. The former gives a finer clot; the latter inhibits the coagulation

5. Clotting of Blood.—Study the effects of temperature; of defibrination; of magnesium sulphate; of the addition of oxalate or citrate; and of calcium. Sodium fluorid, formaldehyd (1 : 400), and leech extract retard or prevent the coagulation. Peptone renders the blood non-coagulable when it is injected intravenously; but not when it is added to shed blood.

6. Citrates or Tartrates, when added to Calcium in the molecular proportion of 3 : 1, render the latter inactive without precipitating it. The calcium is no longer precipitated by oxalates, and cannot be utilized in the ferment-reactions.

7. The transformation of sulphur into sulphid, which occurs in the intestine, is effected at least in part by proteids. It is not affected by heat, so that ferments are probably not involved: Throw some pieces of fresh intestine into 20 c. c. of boiling water. Strain into a small flask. Neutralize. Add a pinch of washed sulphur. Stopper, suspending a piece of lead acetate paper from the stopper. In another similar flask place some water, sulphur, and lead paper. Observe that after a time the paper in the intestinal flask becomes blackened through the evolution of sulphuretted hydrogen. (Other proteids give the same result. The experiment is not always successful.)

B. Experiments on the Retarding Action of Poisons.—General Directions.— Equal quantities of the solutions of the ferment and the test object are placed in test-tubes. These are made of twice the optimum strength in acid or alkali. To each tube is added an equal quantity of the drug to be tested, also of twice the desired strength. Pure Water is added to one of the tubes as a control. The tubes are then stoppered and digested at the proper temperature. Every precaution must be taken to have the conditions perfectly equal for all the tubes and several controls must be made.

The following poisons are suggested. (Remember that the final strength is one-half of that given here):

Water; Quinin hydrochlorid, 1 and 2%; Phenol, 1 and 5%; Alum, 5%; Formaldehyd, 0.2 and 2%; Mercuric chlorid, 0.02 and 0.2%; Alcohol, 2, 10, and 50%; Saturated aqueous solution of salicylic, benzoic, and boric acid, and of salol; Hydrocyanic Acid, 2%; Caffein, 0.02%.

8. Saliva.— Use a mixture of 2% boiled starch and saliva. Add the poisons. Incubate at 40° C. for an hour. Add an equal volume of 10% NaOH. Plunge all the test-tubes simultaneously into a boiling water bath. Examine the depth of color.

9. Pepsin.— Use a 0.1% solution of U. S. P. pepsin in 0.4% HCl. Add a Metts' albumen tube to each test-tube. Add the poisons. Incubate at 40° C. for a day and note the amount of albumen which has been dissolved.

10. Trypsin.— As in 9, using a 0.1% solution of pancreatin in 2% Na_2CO_3, with the addition of enterokinase.

11. Oxidase.— Guaiac resin assumes a blue color when oxidized. This oxidation occurs even when the resin is suspended in plain water, but very slowly. It is greatly accelerated by oxidizing ferments (oxidases), which are present in all living protoplasm. One may use diluted defibrinated blood, or potato peelings or fresh lettuce leaves pounded with sand and water and strained. These are placed in test-tubes, with a drop of fresh guaiac tincture (U. S. P.). The poison solutions are then added and the depth of the blue color noted from time to time. Prussic acid is especially effective in retarding this oxidation. Caffein hastens it somewhat. It is very greatly accelerated by hydrogen dioxid.

EXERCISE 20.—GENERAL PROTOPLASMIC POISONS.—ACTION ON MONOCELLULAR ORGANISMS.

Study in connection with Chapter VII and XVII. Also consult Exercise 44.

Explanatory.— Poisons are divided into two groups: (1) Those which kill all forms of living tissue to which they may be applied; and (2) Those which act selectively, *i. e.*, which have a much stronger action on some tissues than on others. The first are called *general protoplasmic poisons;* the second, *muscle-nerve poisons.*[1]

The general protoplasmic poisons are again subdivided into those which act also on dead proteids — the corrosives — and those which act exclusively on living cells — protoplasmic poisons in the restricted sense.

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[1] Their action is not necessarily restricted to muscular and nervous tissue, as the name would imply. It may also be exerted on gland cells &c. The distinctive feature of the classification is, that the action is selective.

The effects of general protoplasmic poisons are studied most conveniently on monocellular organisms.

The boundary between the general protoplasmic poisons and the muscle-nerve poisons is not sharply defined. Many of the typically selective poisons, such as strychnin, are toxic to all tissues when they are used in sufficient concentration. The protoplasmic poisons also show some specialization. Quinin, for instance, kills ameboid cells much more readily than it does bacteria. All protoplasmic poisons, however, are to some extent bactericidal: and all antiseptics can be counted in this group.

Experiments (*Optional.*)— **1. Bacteria.**— The estimation of the antiseptic power of protoplasmic poisons belongs to the domain of bacteriology. The drugs mentioned in the preceding exercise may be tried.

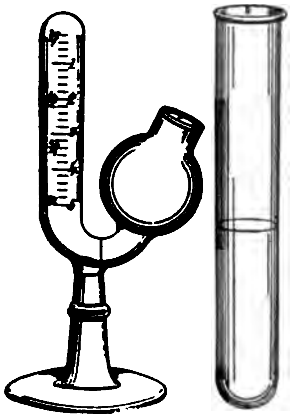

Fig. 121.— Fermentation tube.

2. Yeast Cells.— (Demonstration.)— Make a fairly concentrated suspension of yeast in 35 c. c. of 5% glucose solution. Shake and measure out three portions of 10 c. c. into test-tubes. Add to (*a*) 10 c. c. of ½% *quinin solution;* to (*b*) 10 c. c. of ½% *strychnin;* to (c) 10 c. c. of water. Fill them into the fermentation tubes (Fig. 121), and set into the bath at 37° until the upright of tube in (*c*) is almost filled with gas. Note how much gas has been evolved in the other tubes; it will be seen that the quinin has the greater restraining action, but the strychnin also hinders the gas formation somewhat.

3. Infusoria.— Macerate a little hay in water for several days, until infusoria are developed. Place a drop of the infusion on a slide and note with the microscope the movements of the infusoria. Place a drop on each of four slides; add to slide (*a*) a drop of ½% *quinin;* (*b*) ½% cocain; (c) ½% *strychnin;* (*d*) $^1/_{10}$% $HgCl_2$. Cover with cover-glasses (interposing a hair to prevent pressure) and examine at once, and then every ten minutes. The $HgCl_2$ kills the infusoria at once, fixing them in their original elongated shape. The others act much more slowly; the movements become more sluggish, and finally the infusoria contract to round balls and die.

The quinin kills first, then the cocain, and last the strychnin. The observations need not be continued after the animals in the cocain have died.

4. The **action of poisons on leucocytes** can also be studied, either with the warm stage, or more simply by leaving them with finely powdered animal charcoal for an hour at 37° C., and examining whether they have taken up the pigment. (If they have not been injured, about 8% will be found phagocytic.)

5. Quinin on Emigration of Leucocytes.— Dispose a frog for the observation of the mesenteric circulation (see page 796). Apply some 1% solution of quinin hydrochloric to a limited space. Observe the effect. Place an unpoisoned portion in the field and inject 1 or 2 c. c. of the quinin solution in the dorsal lymph-sac. Compare the results with figure 73, page 332. Continue the observation for half an hour, if necessary.

EXERCISE 21.— EFFECTS OF DRUGS ON HEMOGLOBIN.

Study in connection with Chapter VII or XVII.

Explanatory.— The blood pigment, hemoglobin, gives a characteristic absorption spectrum (Fig. 79, page 378.) It is easily altered by chemic reagents, with corresponding modifications in the spectrum. This is sometimes important in diagnosing poisoning. (It is not necessary to repeat those experiments which have been performed in the physiology course.)

Experiments.— Use a solution of four parts of defibrinated blood[1] in 100 parts of water or of $^1/_{10}$% NaOH.

1. Oxyhemoglobin.— Place some of the solution in a test-tube and examine with the spectroscope and note the two dark lines, between yellow and green (diluting if necessary).

2. Reduced Hemoglobin.— Add a few drops of fresh ammonium sulphid to the test-tube: notice the darker color and observe the single band.

3. Carbon Monoxid Hemoglobin.—(*a*) Pass some coal gas through a little of the original blood. The spectrum is almost unchanged. The color is a deeper, brighter red. Add a few drops of the sulphid: The double band persists; there is no reduction.

Carbon Monoxid, which is the principal toxic ingredient of coal gas, acts by combining so firmly with hemoglobin that it cannot take up oxygen. Death therefore occurs by asphyxiation. The combination is broken up by a great excess of oxygen, so that recovery is possible with artificial respiration or the inhalation of oxygen.

The skin and mucous membranes are of a bright, cherry red color in carbonic oxid poisoning; whereas they are blue in ordinary asphyxia.

The color of the blood itself is the most certain proof of carbonic oxid poisoning. The test is performed as follows:

(*b*) Add a drop of undiluted blood to each of two test-tubes, half filled with water. Pass a stream of coal gas through one of the tubes, and note that the color changes from amber to carmin. In suspected poisoning, a drop of blood is drawn from the finger, diluted as in the above, and compared with the control tube. The depth of the red color permits an approximate estimate of the degree to which the hemoglobin is saturated with CO.

4. Alkali Hematin.— Add a few drops of sodium hydrate to the diluted blood. The color deepens; the spectrum changes to a broad, diffuse band.

5. Acid Hematin.— Add a little dilute acid to the diluted blood; the color becomes brownish, and some precipitation may occur. The spectrum shows a sharp line in the red.

The blood in the vessels does not show acid or alkali hematin, even in severe poisoning; but they may be discovered locally; *e. g.*, in the vomit.

6. Methemoglobin.— Put some of the diluted blood (about 15 c. c.) into a series of six test-tubes. Add the reagents mentioned below, and note changes in color and spectrum at once. If none appear, place in a water bath at 40° C. and observe every half hour.

1. 25 drops saturated $KClO_3$.
2. " " 5% Pot. ferricyanid.
3. " " 10% $NaNO_2$.
4. " " 1% $KMnO_4$.

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[1] Dog's blood contains on an average 15% of hemoglobin; beef's blood, 10%.

S. M.— Waterbaths, diluted blood (1 Liter), undiluted defibrinated blood, 10 c. c.

5. 25 drops Phenylhydrazin.
6. " " 10% Pyrogallol (Methemoglobin spectrum and precipitate of Hemogallol).

Methemoglobin has a rather brown color and shows a sharp band in the red, closely resembling acid hematin (see figure).

To one of the test-tubes which shows a good methemoglobin band, add a little ammonium sulphid: the reduction occurs comparatively slowly, and more of the reagent is required.

Explanatory.— Methemoglobin is a peculiar modification of oxyhemoglobin. It differs from the latter in being less readily reduced. The conversion of any considerable proportion of the blood pigment into methemoglobin therefore leads to asphyxia, characterized by intense cyanosis. This conversion takes place even more readily in the body than in the test-tube; the chlorate and the coal tar products are especially apt to produce the effect in living mammals, whilst they act sluggishly on shed blood.

The conversion of hemoglobin into methemoglobin can be effected by: Oxidizing agents (1, 2, 4), reducing agents (3, 6), coal tar derivatives (5). The rapidity of the conversion varies considerably; in 2, 3, and 4 it is almost instantaneous: in 1 it may require several hours; the others are intermediate. The results are somewhat different in the intact mammals, ClO_3 and the coal tar products being quite active. (5) may also show the band of reduced hemoglobin.

7. Cyan-Hemoglobin.— Add a drop of 2% hydrocyanic acid to some of the diluted blood, and to some methemoglobin solution. The first shows no change. In the second, the color brightens and the spectrum changes so as to resemble reduced hemoglobin (see figure). This reaction may be used as a test for hydrocyanic acid or for methemoglobin.

This peculiar combination of cyan and hemoglobin does not occur normally during life — since the blood does not contain methemoglobin. The latter may be formed after death, especially in ecchymotic areas; and the bright red color of these spots is a characteristic feature of cyanid poisoning.

Formulate conclusions on the whole exercise.

EXERCISE 22.— EFFECTS OF DRUGS ON RED BLOOD CORPUSCLES.

Study in connection with Chapters VII, XVIII, or XXIV.

Explanatory.— The pigment of the corpuscles may be altered in the manner studied in the preceding exercise. The structure of the corpuscles may also be affected by poisons. The principal changes are hemolysis (laking), crenation, and agglutination.

A. Hemolysis (Laking).— This consists essentially in a solution of the corpuscles; after a preliminary swelling, the hemoglobin and salts pass from the corpuscles into the serum (which therefore becomes colored). The stroma can at first be distinguished, especially by staining, as colorless "ghosts," floating in the amber colored fluid. These also are eventually dissolved.

Laking agents act by increasing the permeability of the cell-envelope. This consists largely on fatty (lipoid) substances, especially lecithin and cholesterin. All fat solvents — ether, alkalies, saponin, etc.— therefore produce laking. They may be robbed of this action by previously saturating them with oil. The bacterial *hemolysins* probably act analogous to saponin.

The entrance of water into the cell also causes laking. This occurs

S. M.— Water baths, diluted blood (1 Liter), undiluted defibrinated blood, 10 c. c.

when the cell is laid in water, or in any solution of a weaker salt-content than serum. The result is due to osmosis (see below).

Urea is an exception: it does not prevent laking.

B. Stronger salt solutions, on the other hand, withdraw water from the cell, and shrivel it, producing "**crenation.**"

Other cells behave in a very similar manner.

C. Agglutination consists in the clumping of corpuscles. It is probably due to a change in the viscidity of the envelope. It may be produced by dilute acid and some other chemic agents, but is seen most typically with certain toxins, the *agglutinins.*

Experiments:

Record the results and summarize the conclusions.

I. In Test-Tubes:

Put into 8 *perfectly clean* and *dry* test-tubes:

(*a*) 5 c.c. of 0.9% sodium chlorid.

(*b*) 5 c.c. of 0.9% sodium chlorid containing $^1/_{10}$% of crude Saponin.

(*c*) 5 c.c. of 0.9% sodium chlorid containing $^1/_{10}$% of crude Saponin and 5 drops of cottonseed oil.

(*d*) 5 c.c. of 0.9% sodium chlorid and 20 drops of ether.

(*e*) 5 c.c. of 0.9% sodium chlorid containing 1% of urea.

(*f*) 5 c.c. 1% urea.

(*g*) 5 c.c. 2% Na_2CO_3.

(*h*) 5 c.c. of distilled water.

(*e* and *f* must be freshly prepared.)

Add to each tube 2 drops of defibrinated blood and shake. Observe after half an hour in which tube laking has taken place, as denoted by the clearness of the mixture, or the color of the supernatant fluid.

Isotonic solution of sodium chlorid (*a*) is indifferent, and does not cause laking. The addition of sapotoxin (*b*) dissolves the fatty envelope, and thus allows laking. If oil is added, (*c*) the sapotoxin is bound and cannot act on the corpuscles, and there is no laking. (In the body, the cholesterin and lecithin of the blood act as protectives in this way.) Either (*d*) and other fat solvents, as also alkalies (*g*) also cause laking by dissolving the fatty envelope. Water (*h*) injures the corpuscles by removing the salts. Urea (*f*) acts like water. In either case the addition of salt in isotonic proportion (*a* and *e*) prevents laking.

II. Microscopic:

(*a*) Place a drop of defibrinated blood on a slide under a cover-glass. Examine with the medium power of the microscope. Add to one edge a drop of 2% saponin in 0.9% NaCl, strongly tinged with methylen blue. It will be seen that the corpuscles lose their hemoglobin, but the stroma ("ghosts") remains for a considerable time, and can be discerned faintly by the methylen-blue stain.

(*b*) Repeat the last experiment, but add water tinged with methylen-blue in place of the saponin solution: The corpuscles are seen to swell and to lose their hemoglobin, but more slowly than with the saponin.

(*c*) Repeat the experiment, adding amyl-alcohol in place of the water: Move the cover-glass a little: the corpuscles become agglutinated into small clumps and then lose their hemoglobin.

(*d*) *Hyperosmotic Solutions on Blood Corpuscles.*— To a drop of defibrinated blood under the microscope add a drop of saturated salt solution: The corpuscles shrivel and become crenated, by the abstraction of water. Similar phenomena can be seen in most cells, *e. g.*:

(*e*) *Plasmolysis* (Optional).— Add some saturated salt solution to

S. M.— Microscope (medium power); slides and covers. Spirogyra. Fresh defibrinated blood.

a few threads of spirogyra (a green fresh-water alga) under the microscope: The protoplasm retracts from the cell wall.

(*f*) *Agglutination by Vegetable Toxin.*—On one end of a slide place a rather large drop of 0.9% NaCl; on the other end, a similar drop of 0.1% ricin in 0.9% NaCl. Add to each a small drop of defibrinated blood, cover, and examine with the microscope after fifteen minutes: The corpuscles in the ricin solution will be "agglutinated" into clumps. Many toxins, and the sera of foreign species, have a similar action.

EXERCISE 23.—PHYSICAL PHENOMENA OF OSMOSIS.

Study in connection with Chapter VII or XXIV.

The physiologic effects of osmosis are studied in Exercises 46 and 70.

Explanatory.—It was seen in the preceding exercise that the protoplasm of cells takes up water and swells when they are placed in dilute solutions: whilst it loses water and shrinks when they are placed in strong solutions of salts, and indeed, of most soluble substances. This process is called *osmosis*. In order that osmosis may occur it is necessary that the two solutions (in this case the protoplasm and the salt solution) have a different concentration; and that they are separated by a membrane (the cell wall) which is permeable to water, but not to the dissolved molecules. A membrane of this kind is called *semipermeable*. A membrane which is not quite impermeable to the dissolved molecules but which interposes more resistance to them than it does to water, may be termed *partly semipermeable*. Most, if not all, cell walls belong to the last class; so does parchment. These membranes often possess a different degree of permeability for different salts.

The molecules of a substance in the state of solution behave precisely like the molecules in a gas (Van't Hoff's Theory), and obey the same laws (Gay-Lussac's, Avogadro's, Boyle-Mariotte's). They therefore tend to distribute themselves evenly through the space at their disposal, *i. e.*, through the solvent. When they are prevented from doing so, by the interposition of a semi or partly semipermeable membrane, they exert a pressure which is strictly proportional to the number of molecules present in a unit of space, and independent of the nature of the molecules. This is called the *osmotic pressure*.

A *mol* (molecular weight expressed in grams) dissolved in a liter of water exerts the same pressure as a mol of gas confined in the same space, *i. e.*, 22.34 atmospheres at 0° C. This osmotic pressure can only be realized under the above conditions—*i. e.*, when two solutions are separated by a semipermeable membrane. If the two solutions have the same *molecular concentration* (mols per liter), they will be under the same osmotic pressure; they are said to be *isotonic*. If they are of different concentration, the stronger solution will be under a higher pressure; it is said to be *hyperisotonic;* the weaker is *hypoisotonic*. This difference of pressure tends to equalize itself by the passage of the solvent through the membrane, so as to render the two solutions of equal concentration. This changes the volume of the solutions: the weaker solution diminishes, the stronger gains, in volume. This is the explanation of the changes in the volume of the cells in the preceding and following experiments.

The law that the osmotic pressure is directly proportional to the molecular concentration holds strictly only for substances like urea, alcohol, sugar, etc. It needs to be modified for acids, bases, and salts; for in dilute solutions the molecules of these substances fall apart, the fragments acquiring charges of electricity, and being known as *ions* (*Arrhenius'* Hypothesis). The degree of ionization increases with dilution. Each ion behaves physically like an entire molecule. A very dilute solution of NaCl therefore exerts twice the calculated osmotic pressure; sulphuric acid $(\overset{+}{H}\text{-}\overset{+}{H}\text{-}\overset{-}{SO_4})$ three times; sodium phosphate $(\overset{+}{Na}\text{-}\overset{+}{Na}\text{-}\overset{+}{H}\text{-}\overset{-}{PO_4})$ four times, etc. (The + and — indicate the nature of the electric charge which is carried by the ion.) The undissociated molecules and the ions, existing in a solution under given conditions, are called collectively *mol-ions*. It is really the molions, and not the mols, which determine the osmotic pressure.

The experimental determination of the absolute osmotic pressure is beset with serious technic difficulties. It requires the construction of a vessel with strictly semipermeable walls, of sufficient strength to withstand the high pressure.

The Pfeffer cell is the nearest approach; a porous clay cell is filled with copper sulphate and set in a solution of potassium ferrocyanid. The two solutions meet in the pores, and cause a precipitate of the reddish brown copper ferrocyanid, which functionates as a semipermeable membrane. *Osmometers,* thistle-shaped tubes closed with parchment, bladder, or peritoneal membrane, are useful in certain physiologic experiments; but they are only partly semipermeable.

Fortunately, there are other properties of solutions which vary precisely with the molecular concentration, and which are much more easily determined. Such are the boiling point, or most conveniently, the freezing point. Each molion, added to a liter of water, depresses the freezing point of the water by exactly 1.85° C. (Raoult's Law). This depression of freezing point is denoted by Δ. A 1% NaCl solution gives Δ 0.589.

A table of other solutions having the same Δ is given on page 000.

The freezing point can be used for the following **calculations:**

1. **The Molecular concentration** $= \dfrac{\Delta}{1.85}$

2. **The Osmotic pressure** $= \dfrac{\Delta \times 1697.8}{1.85} \times \left(1 + \dfrac{t^\circ}{273}\right)$ cm. of mercury or $\dfrac{\Delta \times 22.34}{1.85} \times \left(1 + \dfrac{t^\circ}{273}\right)$ atmospheres ($t^\circ =$ temperature in degrees centigrade).

3. **The Molecular Weight** $= \dfrac{1.85 \times \text{Gm. per liter}}{\Delta}$ (if no ionization occurs).

4. **The Dissociation Coefficient** (factor *i*) $= \dfrac{\Delta \times \text{molecular weight}}{1.85 \times \text{Gm. per liter}}$

(This factor gives the ratio on molions to mols. It is used for deducing the actual freezing point or molecular concentration, from that which is calculated on the assumption that no dissociation occurred.)

5. **The proportion of ionized molecules** (factor *a*) $= \dfrac{i-1}{n-1}$

i being the factor of the last paragraph; n, the largest number of ions into which the molecules can split (2 for NaCl, 3 for Na_2SO_4, etc.).

Work out the following problems and check the answers:

1. What is the molecular concentration of blood serum, if $\Delta = 0.555$? Answer: 0.3.

2. What is its osmotic pressure at 38° C.? Answer: 580.6 cm. Hg or 7.6 atm.

3. What is the molecular weight of urea, if a 2% solution $= \Delta$ 0.62? Answer: 59.7.

4. What is the dissociation coefficient of a 1% NaCl solution (Δ 0.589; molecular weight, 58.4)? Answer: 1.85.

5. What fraction of the molecules is ionized? Answer: 0.85.

Osmotic Pressure Through Partly Semipermeable Membranes.— It is evident that this cannot reach the theoretic level; for some of the molecules will escape. If the membrane is as permeable to the dissolved molecules as it is to water, there can be no osmotic pressure whatsoever, no matter what the concentration. Such a solution will therefore be hypoisotonic to a solution, the dissolved molecules of which cannot pass the membrane. One may therefore see the paradoxic phenomenon of a weaker solution (of a non-permeating substance) being hyperisotonic to a stronger solution (of a permeating substance). The law, that *equimolecular solutions* (having the same molecular concentration) are isotonic, holds therefore only for strictly semipermeable membranes. The cell membrane of the red blood corpuscles is strictly semipermeable to most substances. The corpuscles are therefore isotonic to a 0.9% NaCl solution, and to equimolecular solutions of most other substances. Urea and ammonium salts are exceptions; they penetrate readily, and their solutions are consequently hypoisotonic and produce laking (see preceding exercise). Many other cells (for instance, those of the kidney) show more numerous peculiarities of penetration (see below).

Solutions of substances with very large molecules always exert a low osmotic pressure, since even the strongest solutions must have a low molecular concentration. To this class belong the *colloids*— gums, proteids, gelatin, etc.

Osmosis is most conspicuous with the substances of small molecular weight, the crystalloids. It is most important in the case of salts; the subject of osmosis is therefor often called SALT-ACTION.

Exercises (Demonstrations)— **1. Determination of Freezing Point.**— This is done by the Beekmann Apparatus (Fig. 122). This consists of a thermometer (*g*), with an arbitrary scale (which must be adjusted for each determination, see below) graduated in 0.01° C. This is supported by a cork in a large strong test-tube (*e*), which may bear a side piece (*f*) for the introduction of ice. The cork is perforated for a platinum stirrer (*h*). The test-tube is supported in a larger tube (*d*), which acts as an air jacket, equalizing the temperature. This sits in a jar (*a*) of freezing mixture, together with a stirrer (*c*) and ordinary thermometer. The principle of the method consists in overcooling the contents of the test-tube until ice forms, when the thermometer column suddenly rises and comes to a standstill at the correct freezing point. The zero point is first controlled by the standard sodium chlorid solution (10 Gms. of dried salt dissolved in a liter of water, $\Delta = 0.589$).

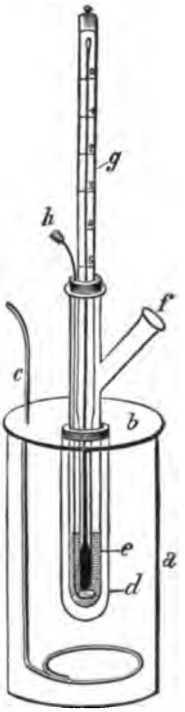

Fig. 122.—Beckmann-Heidenhain's apparatus for determining the freezing-point of a solution.

Fill the outer jar with a freezing mixture of pounded ice and salt.

This is stirred occasionally throughout the determination, and kept at about — 5° C. by the addition of salt or ice. Place the standard sodium chlorid solution in the tube and insert the thermometer, so that the bulb is raised about a centimeter above the bottom of the tube. The level of the solution should be 1 to 2 cm. above the bulb. Plunge the tube directly into the freezing mixture, stirring the solution constantly. The mercury will be seen to recede from the reservoir and descend into the stem; at a certain point it will reverse its motion and ascend. Transfer the tube quickly from the mixture to the jacket-tube, continuing the stirring. When the columns come to a standstill, take a reading: this is merely approximate.[1] Remove the tube and stir until only one or two particles of ice remain melted. Plunge for a moment in the freezing mixture, then into the jacket-tube, and stir until the mercury is constant. Take a reading with a lens, and repeat melting and freezing twice. The readings should not differ by more than 0.003° C. Take the average. Adding 0.589 to the result gives the zero point of the thermometer, from which all other readings must be subtracted. The Δ of defibrinated blood and a sample of urine may now be determined.

2. Hamburger's Blood-Corpuscle Method.— Blood corpuscles are laked when placed in a solution of a certain concentration (about 0.525% NaCl); the relative concentration of solutions may therefore be determined by comparing them with a known sodium chlorid solution. This holds true only if the blood corpuscles are equally impermeable to the observed substance. It may be accepted as correct for most substances, with the notable exceptions of urea and ammonium salts.

Prepare solutions of NaCl, $NaNO_3$, and Urea, all having the same freezing point (1% NaCl; 1.535% $NaNO_3$; 1.89% Urea). Set up a series of clean test-tubes, of about 15 c. c. capacity, and of equal diameter. With a pipette, graduated accurately in $^1/_{10}$ c. c., place in the first 4 c. c. of the NaCl solution and 6 c. c. of water; in the second, 4.5 c. c. NaCl and 5.5 of water; third, 5 c. c. and 5 c. c.; fourth 5.5 c. c. NaCl and 4.5 c. c. water; fifth, 6 c. c. NaCl and 4 c. c. water. Place corresponding dilutions of $NaNO_3$ and of urea in the other tubes. Mix the contents of each tube. Add to each 10 drops of defibrinated blood. Let stand overnight.[2] Note the tube in each series in which there is just perceptible laking. This will be the same for the chlorid and nitrate, but all the urea tubes will be laked.

3. Osmotic changes in the weight of Tissues.— Place the following solutions into evaporating dishes:

a. Water.
b. 5% NaCl.
c. 1% NaCl.
d. Urea. } Of the same freezing point as 1% NaCl
e. Sodium Citrate. } see page 822).

Cut a fresh dog's or rabbit's kidney into sections about 1 mm. thick. Rinse a section in 1% NaCl for a moment, dry it superficially with filter paper, and weigh; lay it in solution *a.* Prepare other sections in the same manner, laying them in the other solutions. Leave in the solutions for half an hour, then again dry and weigh the sections. The

S. M.— Beckmann apparatus; salt; pounded ice; 1% NaCl; test-tubes and solutions for Hamburger's method; defibrinated blood; sections of kidney; dishes with solutions for kidney experiment. Analytic balance.

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[1] If this point comes at an inconvenient place of the stem, the thermometer must be taken out and some mercury subtracted or added to the column, by gently shaking.

[2] The preceding part of the experiment may be prepared on the preceding day, only the results being demonstrated.

weights will be changed, the sections having absorbed or lost water through osmosis:

(*a*) increase of weight — water being strongly hypoisotonic.
(*b*) decrease “ “ — 5% NaCl being strongly hyperisotonic.
(*c*) increase “ “ — The protoplasm of the kidney cells is therefore hyperisotonic to 1% NaCl (and consequently to blood serum). It requires about 1.8% of NaCl to keep the weight unchanged.
(*d*) increase “ “ — much larger than in (*c*). Consequently, the kidney cells are easily permeable to urea.
(*e*) decrease “ “ — The sodium citrate penetrates less readily than sodium chlorid.

The experiment illustrates strikingly that the osmotic pressure depends not only on the molecular concentration, but also on the permeability of the cell wall, which is different for each substance, in the kidney. Urea penetrates readily, chlorid less, and citrate still less so.

CHAPTER XXXVI.

EXERCISES ON FROGS AND INTACT MAMMALS.

Preliminary Remarks.— Before starting on this division of the work, the student should read the methods (pages 792 to 820); also the remarks on note-taking (page 823). The contents of the lockers should be checked (Table XXIII, page 785).

The conditions in animal experiments are much more complicated than in chemic work. The student must learn to fix his attention on the main phenomenon, without neglecting anything whatsoever. The more functions he can embrace in his observations, the more valuable will be the results and the training.

On account of slight differences in dosage, in the surrounding conditions and in the idiosyncrasy of the animals, the results are often atypical. This should be reported to the demonstrator; for these abnormalities sometimes demonstrate some fact of elementary importance, which it might be difficult to reproduce by intentional experiments. They should be shown to the class. The demonstrator should see to it that every member of the class sees the typical effects; if not in his own experiment, then at least by the demonstration of the results of another set. The time elapsing between the administration and the occurrence and disappearance of the symptoms should be particularly noted.

The class may be divided into small sets of 3 students, four of which should be in care of a demonstrator. Two sets may share a locker. It is not necessary that every student perform every experiment; in many instances, it is more profitable to divide the exercise between the sections. Every student, however, should *see* each experiment.

A class reporter should be appointed each laboratory day. He should be relieved from the performance of the experiments, but should collect and summarize the results and conclusions, and read his report at a weekly meeting. This report should be criticized by the class and instructor and should count in the final grade. The conclusions should be restricted to the results of the experiments. The reports should be filed for reference by future classes.

EXERCISE 24.—THE ABSORPTION OF DRUGS.

Exercises 24 to 29 may be studied in connection with Chapter VII.

The experiments may be demonstrated, or divided amongst the students.

Read up the administration of drugs, pages 803 to 805.

Explanatory.— Most drugs must be absorbed before they can produce any action. This holds particularly for drugs which act *systemically; i. e.,* on the body cells (in contradistinction to the *locally* acting drugs, the effects of which are confined to the place where they are applied, or to reflexes originating from this point). The subject of absorption has therefore a great practical importance. Absorption may occur from most of the surfaces of the body, but with very different facility. The *intact skin* of mammals is almost impermeable to watery solutions, but absorbs oils and volatile substance (consult exercise 13, No. 10). The skin of frogs, however, absorbs watery solutions readily. In mammals, the most usual channels of absorption are the alimentary canal, the subcutaneous and muscular tissue, and the lungs. The rapidity of absorption varies with the nature of the drug and the place of administration. It is generally proportional to the volatility and solubility of the drug. Volatile substances are absorbed most rapidly from the lungs; watery solutions from intramuscular and subcutaneous injections; resins and oils from the intestinal tract. The absorbability from the different portions of the alimentary canal varies for different animals and drugs. It is generally most effective from the small intestine; less so from the stomach and rectum. In man, the stomach generally absorbs better than the rectum; the reverse is true of the rabbit. The uninjured urinary bladder is practically impermeable, whilst the mucosa of the urethra is a good absorbing surface. Most mucosæ absorb readily.

Absorption is retarded by the presence of fats or colloids, gums, proteids, or "extractives."

Experiments: (To be Demonstrated).— **I. Absorption of Soluble Drugs is Generally More Rapid When They are Given Hypodermically, Than When They are Given by Mouth.**— Give to a rabbit 1.0 mg. per Kg. of *strychnin* sulphate (1.0 c. c. per Kg. of $^1/_{10}$%) hypodermically, and to another rabbit the same amount by the stomach-tube. The first rabbit shows the typical strychnin convulsions; the second shows very little effect. Draw a sketch of the typical tetanic condition.

II. Drugs Which are Insoluble in Water May be Absorbed More Efficiently from the Stomach.—Give to a dog 1 c. c. per Kg. of fluidextract (diluted with two volumes of water) of *Cannabis Indica* hypodermically, and to another dog the same dose by stomach-tube. The former animal shows little effect beyond local irritation, the latter shows the typical effects of the drug (ataxia and sleep, possibly preceded by nausea and vomiting).

Materials Needed: (for entire class).— 3 small rabbits; 3 small dogs; 2 guinea pigs; 1 frog; large hypodermic syringe and needle; graduate; stomach-catheter and bulb. $^1/_{10}$% strychnin sulphate (35 c. c.); 1% (5 c. c); Fluidext. Cannabis Ind. (20 c. c.); Nicotin (few drops); 2% HCN (fresh) (5 c. c.); $^1/_{10}$% strychnin sulphate in 25% mucilage (5 c. c.).

III. Absorption May be Extremely Rapid, Even When the Drug is Given by Mouth.— 1. Place two drops of *nicotin* on the gums of a dog.

2. Inject 5 c. c. of 2% *HCN* into the mouth of a rabbit or dog. Notice the very rapid onset of the effects. (The symptoms are quite similar in both cases, and consist in nausea, convulsions, severe prostration. Death may occur, the respiration stopping before the heart; or the animals may recover.) (Fig. 52, page 185.)

IV. Absorption is Impaired by Colloids.— Inject into a guinea pig 5.0 c. c. per Kg. of a $^1/_{10}$% solution of *strychnin* sulphate in water; and into another animal the same relative quantity of strychnin dissolved in a 25% mucilage of acacia. Note that the first animal shows the greater effects.

V. Absorption From the Frog's Skin.— Paint some 1% strychnin over the intact skin of a frog. The animal soon goes into convulsions, which are typical of this poison.

Absorption may also occur from the lungs (recall the phenomena of ether and chloroform anesthesia) *and from the rectum* consult Exercise 26, No. 2, H_2S; Exercise 61, No. 1, Urethane.

Not all Soluble Substances are Absorbed from the Alimentary Canal.— Consult Exercise 63, No. 1 ($MgSO_4$).

Summarize the actions of Cannabis Indica, Chapter XXXVIII, No. 1.

Optional Experiments:

VI. The *absence of absorption from the rabbit's stomach or bladder* may be demonstrated on anesthetized rabbits by exposing these viscera, tying the openings, and injecting 25 mg. per Kilo of strychnin into the interior (5 times the fatal dose per mouth). This produces little or no effect. When the same dose is placed in the intestine, the animal succumbs quickly.

VII. The *comparative efficiency of intravenous and intramuscular injection* may be shown by connecting an anesthetized rabbit for blood pressure and injecting 0.4 c. c. of 1 : 1,000 adrenalin, first subcutaneously; and after a time a second dose the pectoral muscles. The subcutaneous injection is almost ineffective. The intramuscular injection causes a considerable rise of blood pressure.

EXERCISE 25.— THE EFFECTS OF DEMULCENTS AND EMOLLIENTS.

Read up Reflex-time, page 795.

Explanatory.— Viscid substances lessen the absorption and the local actions of drugs. They are used therapeutically as "soothing" agents, to lessen inflammation. Those which are used especially on mucous surfaces (mainly gums and other colloids) are called *demulcents;* those which are used on the skin (oils and fats) are termed *emollients.* Glycerin belongs to both classes, but is also somewhat irritant, by abstracting water.

The action of these substances is due to their viscid character. They form an indifferent protective coating, which prevents drying and the access of irritant substances or bacteria. Even when the drug is added directly to the solution, they hinder its access to the tissues by preventing currents in the solution.

The effect of these substances on absorption was studied in Exer-

Materials Needed: (for the entire class).— 2 frogs; frog-tools and hook; jar of water; capsule with 0.1% HCl and another with 0.1% HCl in 15% acacia. 1% citric acid in 10% starch paste and in water (25 c. c. of each).

cise 24, No. 4; and in Exercise 18, Nos. 9 and 10. These should be consulted.

Experiments:

1. **Colloids lessen the Effects of Irritants.**— Decapitate two frogs, and note the *reflex-time* of each on dipping the leg in 0.1% *HCl.* Wash off, dip the leg of one again in 0.1% HCl, the other in a solution of 0.1% HCl in 15% Gum Arabic. The reaction time is delayed by 30 to 100 seconds.

2. Observe that a 1% solution of citric acid in 10% starch paste tastes much less acid than a watery solution of the same strength.

Summarize the effects of Demulcents and Emollients in Chapter XXXVIII, No. 2.

EXERCISE 26.— THE EXCRETION OF DRUGS.

Explanatory.— Drugs may be excreted by various channels; gases and volatile drugs are excreted mainly by the lungs; metals by the intestinal cells; most substances, however, especially salts and alkaloids, are excreted in greatest quantity by the urine. The saliva, bile, skin, and milk may also aid in excretion; but generally these play a very subordinate rôle.

A knowledge of the excretion of drugs has considerable practical importance; it teaches how frequently the drug must be administered to maintain a continuous action; it also indicates how to hasten the elimination of poisons.

The elimination of drugs by the urine was studied in Exercise 13. This should be consulted.

Experiments:

1. **Elimination by the Saliva** (to be assigned).— (*a*) Take a capsule of 0.3 Gm. of potassium iodid. Test the saliva every ten minutes for the presence of iodid, by Exercise 13, No. 8.

(*b*) Take a capsule of 0.3 Gm. of salol, collect the saliva every ten minutes, and test for salol by Exercise 13, No. 2.

Report the results to the class.

2. **Volatile Drugs may be Excreted by the Lungs.**— (Demonstration.)— Hold a paper saturated with lead acetate before the nostrils of a rabbit; note that the paper is not blackened; now pass some H_2S into the rectum; the paper becomes blackened (the H_2S being absorbed from the rectum and excreted by the lungs). If the dose of H_2S has been excessive, the rabbit may show paralytic and convulsive effects. (The experiment is not quite conclusive, for the gas might have reached the paper through the esophagus.)

Not all gases, however, are capable of excretion by the lungs (compare Exercise 51, No. 3, Ammonia).

3. (Optional).— **Time Required for Excretion by Urine and Saliva.**— (To be assigned.)— (*a*) Take 0.3 Gms. of *KI,* dissolved in water. Examine the urine and saliva by Exercise 13, No. 8, every hour for 5 hours, then three times a day for two days. Report the results.

(*b*) Take 0.3 Gms. of *Salol,* powder, and proceed as in I, testing by Exercise 13, No. 2, and reporting the results.

(The KI will appear more quickly than the salol, since the former is absorbed from the stomach, the latter almost exclusively from the intestine.) (*c*) Review the excretion of the other drugs used in Exercise 13.

Materials Needed (for the entire class).— Rabbit, H_2S apparatus, rectal tube. Lead acetate paper; capsules of 0.3 Gm. KI of 0.3 Salol; dilute H_2SO_4; starch paste; 10% $NaNO_2$; Ether; Fe_2Cl_6

EXERCISE 27.—DECOMPOSITION OF DRUGS IN THE BODY.

Explanatory.— A considerable number of drugs undergo chemic changes during their sojourn in the body, being oxidized, reduced, hydrolysed, combined, etc. In some cases the substance is absolutely destroyed. Alcohol, for instance, is almost completely oxidized to carbonic acid and water. In other cases the changes are not so profound. The benzol ring always remains intact, but the transformation of acetanilid into paramidophenol illustrate the changes which occur in the side-chains. Benzol derivatives are further excreted as paired compounds, with sulphuric and glycuronic acid.

Chemic reaction between two drugs may also occur within the body — a fact which must be kept in mind.

Experiments:

1. Chemical Reactions with Normal Body-Constituents; Liberation of Iodin from KI by nitrites of the saliva.— (Each pair of students should try this experiment.) — Mix equal parts of 1% KI and 1% H_2SO_4, add a little starch paste, place in three test-tubes and add to:

(*a*) saliva; (*b*) boiled saliva; (*c*) water. *a* and *b* both turn blue, whilst *c* remains unchanged. Since the reaction is not destroyed by boiling, it cannot be due to ferments. (It is caused by the presence of *nitrites* in the saliva; the depth of color varies greatly in different individuals.)

2. Chemical Reactions Caused by the Presence of Other Drugs. Administer to a rabbit 50 c. c. of 1% *KI* by the stomach-tube. (There may be some depression from the manipulation.) In an hour dust a little calomel into the eye of this, and of a normal rabbit. The iodid rabbit manifests greater irritation at once. In an hour, the normal rabbit shows no effect from the calomel; but in the iodid rabbit there is intense conjunctival congestion and edema. (*Calomel* should never be used with iodids.) Hg_2Cl_2 and KI react together, resulting finally in the yellow HgI_2, which is as irritant as $HgCl_2$ ($Hg_2Cl_2 + 2KI = HgI_2 - Hg - 2KCl$).

3. Vasoconstrictor Action; Treatment of Conjunctivitis.— The above rabbit may be utilized for demonstrating the following: Apply to the inflamed conjunctiva a drop of 1% *cocain;* the congestion diminishes at once, and the pupil dilates. The effect is only short. When it has passed off, apply a drop of $^1/_{100}$% *adrenalin;* vasoconstriction; this effect also passes off. Apply a drop of $^1/_{10}$% hydrastinin hydrochlorid; vasoconstriction, which is somewhat more lasting. Dust some orthoform in the eye. This will greatly lessen the pain.

Summarize iodid excretion in Chapter XXXVIII, No. 3.

Materials Required (for entire class).— 1% KI plus 1% H_2SO_4, with a little starch paste (75 c. c.); 1% KI (50 c. c.); 2 rabbits; stomach-catheter and bulb; calomel (1 Gm.); camel's hair brush; a small quantity of 1% cocain; $^1/_{100}$% adrenalin; $^1/_{10}$% hydrastinin; orthoform.

EXERCISE 28.— RACIAL IDIOSYNCRASY.

Explanatory.— Idiosyncrasy is the term applied to an abnormal reaction to a drug. The abnormality is generally quantitative only; but it may appear qualitative, by bringing into prominence some action of the drug which is ordinarily so small as to escape observation. Most instances of idiosyncrasy may therefore be brought under the headings of exaggerated susceptibility or tolerance. These may be congenital or acquired. Some are readily explained by anatomic or physiologic peculiarities. Others are due to differences in the absorption, excretion, or destruction of the poison. Many phenomena of idiosyncrasy have not yet been satisfactorily explained. The continued administration of a drug often alters the susceptibility of the patient to its action: this may be diminished (*habituation*) or increased (*cumulative action*). Congenital idiosyncrasy may be individual or racial. The student will probably encounter some examples of individual idiosyncrasy in the course of his future work. The following experiments refer to racial idiosyncrasy:

Experiments.— 1. Inject into a dog and into a rabbit 5 mg. per Kg. of *atropin* sulphate (0.5 c. c. per Kg. of 1%) hypodermically. Observe the pulse, pupils, respiration, and the general symptoms. The effects are very much greater in the dog than in the rabbit (the heart rate is quickened by paralysis of the vagus endings; the respiration is first increased, then diminished. The general effects are first excitant, later depressant; the pupils are dilated through paralysis of the oculomotor endings). Let the rabbit inhale a little ammonia, whilst feeling the heart beat: the heart is not stopped, as it would be in normal animals.

The reason of the general resistance of the rabbit (and other herbivorous animals) to atropin is not known. One peculiarity, however, is easily explained. It will have been noted that the pulse-rate is greatly quickened in the dog, but scarcely, if at all, in the rabbit. This is because, in the dog, the heart is normally kept slow by the tonic activity of the vagus center. This is cut out by atropin. These tonic impulses are very weak or absent in the rabbit, so that their abolition does not alter the heart-rate. The ammonia experiment shows that the atropin has paralyzed the vagus, in the rabbit as well as in the dog.

2. Read page 799 for method of exposing the heart. Apply some (10%) infusion of *digitalis* in 0.75 NaCl solution to the exposed heart of a pithed toad and frog, and notice that the effect on the frog is much greater. (Observe that the heart is slowed, and the systole increased, peristaltic waves and arythmia become apparent, and the heart may be arrested in systolic standstill, as a small white lump.)

The skin of the toad secretes a poison with an action analogous to digitalis. The tolerance of this animal is therefore somewhat analogous to habituation.

3. Inject into a dog and into a rabbit 10 mg. of *apomorphin* hydrochlorid (1 c. c. of 1%) hypodermically; the dog vomits, the rabbit does not. The rabbit may show signs of excitement.

The reason for the tolerance of rabbits to apomorphin is found in the fact that rodents are incapable of vomiting.

4. Compare the action of *morphin* on different animals. (Consult Exercise 40, No. 1.) The reason for these peculiarities lies perhaps in the different degree of development of the central nervous system.

Materials Required (for entire class).— 2 small dogs; 3 small rabbits; 1 frog; 1 toad; 1% atropin sulphate (15 c. c.); 10% infusion digitalis in 0.75% NaCl (5 c. c.); 1% apomorphin hydrochlorid (10 c. c.); large hypodermic syringe and needle; 2 frog boards, dissecting tools, pins.

EXERCISE 29.— TREATMENT OF POISONING.

Study in connection with Chapter V, page 88.

Explanatory.— The main features of the treatment of poisoning consists in:

(1) Chemic precipitation, neutralization, or destruction of the poison.
(2) Removal of the poison.
(3) Physiologic antidotes.
(4) General supporting measures.

All treatment must be as prompt as possible.

(1) *Chemic Antidotes.*— These have been discussed in Exercise 14, which should be consulted.

(2) *Removal of the Poison.*— This is accomplished by washing, emesis, lavage, catharsis, and diuresis.

(3) *Physiologic Antidotes.*— The effects of depressant drugs are counteracted by stimulants, and vice versa. It must be remembered, however, that the action of stimulants passes readily into depression, which would increase the danger. Antidotes should therefore be given in rather moderate doses. It should also be borne in mind that physiologic antidotes remove only the symptoms, and not the action of the poison. They are therefore useful only when the symptoms are a direct source of danger. In the case of strychnin, for instance, death is due to the direct depressant action of the drug, aided by the exhaustion consequent on the convulsions. Chloral, curare, or artificial respiration, by preventing the convulsions, are able to save an animal from several times the fatal dose, but they are quite ineffective against doses sufficiently large to kill by the direct depressant action of the poison.

(4) *General Supporting Measures.*— The immediate cause of death, with most poisons, consists in failure of the respiration. This should be carefully watched and supported by hot coffee. Should this prove insufficient, artificial respiration must be instituted, and this before the natural respiration has ceased. The patient should be kept warm. Pain (from corrosives, etc.) should be controlled by morphin or the local use of cocain.

Experiments.— Numbers I to V of the following experiments illustrate the general principles of treatment on strychnin. The symptoms of strychnin poisoning may also be studied. Observe the respiration; the rectal temperature (page 820); the increased reflex excitability; the type of the convulsions, which occur especially by reflex stimulation (jarring the table); make a sketch of the position of the animal during the convulsion. The spasm is at first clonic (*i. e.*, intermittent), then tetanic (fixed), then again clonic. The animal is paralytic between the convulsions. Note the respiration during and between the convulsions. In case of death, observe that the respiration stops before the heart. Rigor sets in very early (as with all convulsant poisons). If the animal recovers, keep under surveillance for several hours, as a relapse may occur.

Strychnin is not absorbed from the stomach of rabbits; so that the

Materials Needed (for 18 students).— 6 small weighed rabbits of approximately equal size; 6 stomach-catheters and bulbs; hypodermic syringe and needles and capsule; six 10 c. c. measuring pipettes; six 25-c. c. graduates; catheter and glass syringe. $^1/_{10}$% strychnin sulphate (75 c. c.); 1% $KMnO_4$ (50 c. c.); 5% Diuretin (30 c. c.); 10% Chloral (18 c. c.); 50% Alcohol (30 c. c.); 1% Caffein (10 c. c.) (This is preferred to the citrate, as being less irritant.)

poisoning occurs only when the alkaloid reaches the intestine. The symptoms therefore occur much later than they do in man, being delayed for half an hour or longer. The passage from the stomach into the intestine occurs gradually, and at a different rate in different animals. A variable amount may therefore be excreted before all of the poison has been absorbed. This makes the fatal dose somewhat uncertain. The average fatal dose of strychnin sulphate for rabbits, by the stomach, may be placed at 4.25 mg. per Kg. A surely fatal dose of 6 mg. per Kg. is used in these experiments. On account of the differences in absorption it may happen that some of the animals which have received antidotes show more severe effects than the control; but this is altogether exceptional. The permanganate alone invariably prevents all symptoms.

One animal may be assigned to each set.

Experiments.— I. Control Rabbit.— Inject 6.0 mg. per Kg. of the *strychnin* sulphate (6 c. c. per Kg. of $^1/_{10}$ %) by the stomach-tube.

II. Chemic Antidote ($KMnO_4$).— Administer the same dose as in I and follow it immediately with 15 c. c. per Kg. of 1% $KMnO_4$. The permanganate destroys the strychnin by oxidation.

III. Physiologic Antidote (*Chloral*).— Administer the same dose as in I and follow it immediately by 0.4 Gm. per Kg. of chloral (4 c. c. per Kg. of 10%). Chloral depresses the central nervous system and thus prevents convulsions. This dose of chloral would lower the temperature in normal animals; strychnin prevents this, although it has itself very little direct action on temperature.

IV. Artificial Respiration.— As in I, followed after half an hour by gentle artificial respiration, which is continued for one hour. The artificial respiration acts partly by preventing asphyxia, which is an important contributory factor in the death from strychnin. It also lowers the reflex excitability of the nervous centers, and thus diminishes the convulsions.

V. Elimination.— Inject into the stomach 0.5 Gm. per Kg. of *Diuretin* (10 c. c. per Kg. of 5%) (this may be done before the demonstration). Follow this in half an hour by strychnin as in I. Wash out the bladder every 15 minutes (see page 820). The diuretin hastens the elimination of the strychnin; but it is not uniformly successful.

VI. Physiologic Antidote.— Caffein and Alcohol.— Count the respiration and take the rectal temperature. Administer to rabbit by stomach 12 c. c. per Kg. of 50% alcohol. When the paralytic condition is so pronounced that the animal does not move spontaneously, count the respiration. Inject hypodermically 20 mg. per Kg. of the caffein (2 c. c. per Kg. of 1%). The animal revives a great deal in a short time. Take the respiration. Continue the observations; the caffein does not generally suffice to improve the condition permanently. This is an instance of the antidotal effects of a stimulant to a depressant. The recovery of the temperature is an indirect effect, as with strychnin and chloral: the stimulant does not act directly on the temperature, but on the general depression which caused the fall.

For other instances of treatment and antagonism consult:

Exercise 14.— Chemic Antidotes.
" 18 C.— Carbolic Acid, local.
" 22.— Saponin and Oil on Red Corpuscles.
" 55.— Pilocarpin and Atropin on Saliva.
" 54.— Pupil.
" 67.— Intestine.

Exercise 50.— Vagus.
" 59, 5 and 6.— Carbolic Acid and Sodium Sulphate.

Summarize the effects of permanganate in Alkaloidal poisoning, in Chapter XXXVIII, No. 4.

EXERCISE 30.— EMETICS ON DOGS.

Study in connection with Chapters XIV and XXVIII.

Emetics are divided into two classes: Those which stimulate the vomiting center in the medulla directly (*central emetics*) and those which stimulate it reflexly (*local emetics*). The central emetics act at least equally well when they are injected hypodermically. Apomorphin is the principal example. Local emetics act by irritating the sensory endings in the pharynx or stomach. They are effective only if they are administered or excreted by this channel. All irritants belong to this class; but only those are practically useful which have only a slight toxicity, or which act so promptly that they are expelled before absorption can occur.

If a drug produces vomiting when injected into the circulation, and not when it is given by mouth, its action is surely central; and vice versa. If it causes emesis in either case, the relative quantity and the time required are taken into consideration: if it is more efficient by the circulation, its action is, at least mainly, central; and vice versa. The absolute distinction is made by ligating all the vessels of the stomach, exclusive of the nerves: a centrally acting emetic will now be effective only when injected into the circulation, a local emetic only when placed in the stomach.

Emesis, the act of vomiting, is preceded by nausea, and followed by depression. The relative duration of these stages is of great practical importance.

Experiments (Demonstration or Assigned).— **Observations to be Made.**— The onset and duration and symptoms of nausea; onset and frequency of emesis; pulse and respiration of normal animal, in nausea, just before, during, just after, and some time after, vomiting. Note how soon the dog will drink water and eat meat again. Report the results.

Distribution of Work.— Each set may be given one of the experiments.

1. **Apomorphin.**— (Consult Exercise 28, No. 3).— Inject hypodermically 2 mg. per Kg. (0.2 c.c. per Kg. of 1%). Emesis in 3 to 15 minutes, repeated several times. (Central action.)

2. **Zinc Sulphate or Copper Sulphate.**— 50 c.c. of 1% by stomach. Repeated emesis in about 10 to 30 minutes. (Irritation of the stomach.)

3. **Other emetics** may also be used by mouth (optional), such as:
(*a*) Ipecac (2 c.c. of fluidextract).
(*b*) Tartar emetic (20 c.c. of ¼%).
(*c*) Mustard (teaspoonful) in warm water.
(*d*) Ammonium Carbonate (20 c.c. of 5% solution).
(*e*) Senega (5 c.c. of fluidextract).

4. **Paralysis of Vomiting Center.**— Inject 10 mg. per Kg. (¼ c.c. per Kg. of 4%) of morphin, subcutaneously. This will cause vomiting, probably by an action similar to apomorphin (which is a

Material Required (for entire class).— 3 dogs recently fed; hypodermic syringe; stomach-catheter; meat; 10 c.c. and 25 c.c. graduate; 1% apomorphin hydrochlorid (5 c.c.); 1% zinc sulphate or copper sulphate (50 c.c.); 4% morphin salt (5 c.c.).

derivative of morphin). After half an hour, inject apomorphin as in 1. This will be ineffective, as the morphin-stimulation of the vomiting center is followed by a profound depression. All other emetics will be similarly ineffective. This is utilized in experimental technic, when it is essential to have an irritant drug retained in the stomach.

Summarize the effects of Apomorphin, Copper, and Zinc, in Chapter XXXVIII, Nos. 5 and 6.

EXERCISE 31.— CATHARTICS.

Study in connection with Chapter XXX.

Explanatory.— All drugs which irritate the mucous membrane of the intestine increase peristalsis, and thus produce catharsis. Not every irritant, however, can be utilized therapeutically. The irritation must not exceed the required degree; the drug must not be poisonous in cathartic doses; the irritation should be confined to the intestine, and should not involve the stomach.

A number of salts, particularly the sulphates and magnesium, are not absorbed from the intestine. In virtue of their osmotic pressure, they also retain fluid and this acts as a mechanical stimulus. This stimulation is comparatively mild, and is not accompanied by inflammation. The feces are rendered soft or fluid.

Most other cathartics act chemically and are more or less irritant. As a rule, this irritant action is confined to the intestine; the irritant principle being liberated only by the chemic processes in the intestine.

Many cathartics give a green color to the stools. This was formerly attributed to an increased secretion of bile, and these remedies were therefore called "*chologogues.*" The name is still used, although it has been shown that the green color is not due to an increased quantity, but to a lessened decomposition of the bile; the quick propulsion of the intestinal contents leaving less time for bacterial decomposition. Calomel, the most typical of these so-called chologogues, is also antiseptic; it is partly converted into the sulphid, which serves to darken the color still further.

Experiments.— 1. (Optional.)— The student is advised to try on himself the action of cathartics such as Rhubarb, Senna, Cascara, Epsom, Glauber's, and Rochelle Salts, Cream of Tartar, Sulphur, Manna, Castor Oil, Calomel, Compound Cathartic Pill. These can also be tried on animals, if it is desired, using for dogs about ⅕ of the dose for man.

Consult also Exercise 67.

2. Chologogue Action of Calomel (Demonstration).— Place in an incubator some bile in which a knife-point of calomel has been added, and another sample without this addition, for control. The color changes first in the latter sample.

Material Needed.— Incubated bile, with and without calomel.

EXERCISE 32.— GASTROENTERITIS.

Study in connection with Chapter XXVIII.

Explanatory.— The most important phenomena of poisoning by irritants are caused by gastroenteritis. The principal symptoms consist in very severe abdominal pain; profuse vomiting and diarrhea; and reflex collapse. If the irritant is also corrosive, the discharges are bloody or otherwise discolored. The stools are generally very watery.

Refer. to Exercises 15 to 18.

Observations Required.— Keep in cage and collect urine. During life note the vomiting, watery diarrhea, and general depression. At autopsy note the congestion of the abdominal organs, particularly the mucosa of the alimentary canal. Observe the character of the contents, and look for corrosions. Corrosions are most pronounced in the case of the mercury; their absence with colchicum. The latter causes intense congestion in ridges. Observe that the arsenic produces its effects, even when it is given hypodermically (note particularly the fluid contents). The animal usually lives several hours, or longer. The urine of mercury and arsenic will generally contain albumen and casts. The mercury and veratrin animals may recover, but will show erosion of the stomach on autopsy.

As these experiments are necessarily painful to the animal, they should only be demonstrated, or made optional.

Experiments.— 1. Colchicum.— 1 c. c. per Kg. by mouth, to a dog.

The alkaloid of colchicum is practically inactive; but is converted in the tissues of mammals into oxydicolchicin, which is the toxic agent. This explains the long interval between administration and symptoms. The drug is not at all corrosive. It is supposed that it does not irritate directly, but that it merely exaggerates the normal irritability of the intestine.

2. Mercuric Chlorid.— 10 c. c. of $^1/_{10}$% by mouth, to a rabbit.

Notice the white (cooked) appearance and hardness of the gastric mucosa at the autopsy.

3. Arsenate of Sodium.—5 c. c. of 5% hypodermically, to a rabbit.

The symptoms and lesions of arsenic poisoning bear the closest resemblance to those of local inflammation of the alimentary tract. It can be shown, however, that the direct irritant or corrosive action of the poison is entirely inadequate to produce this inflammation, especially when the poison is given hypodermically or intravenously. Its action is really due to a direct paralysis of the capillaries, with increased permeability. This is also the main phenomenon of inflammation. The lesions are therefore identical. A characteristic clinical feature of acute arsenic poisoning consists in the "rice-water" stools — which consist of a profuse watery exudate with shreds of desquamated mucosa.

4. Veratrin.— 1 c. c. of 1% by mouth, rabbit.

Veratrin is one of the very few alkaloids which are directly corrosive.

5. The **corrosion of the stomach** by concentrated acid and alkalies may be demonstrated on deeply anesthetized dogs. Compare Exercise 16.

Summarize the effects of Colchicum in Chapter XXXVIII, No. 7.

Material Required (entire class).— Dog and 3 rabbits; graduate, hypodermic syringe, stomach-catheter. Fluidextract of Colchicum (root or seed), 15 c. c.; 1 : 1,000 mercuric chlorid (20 c. c.); 5% sodium arsenate (5 c. c.); 1% veratrin (5 c. c.).

EXERCISE 33.— NEPHRITIS.

Study in connection with Chapter XXVIII.

Explanatory.— The action of irritants is proportional to their concentration. This is greatest where they enter and leave the body — in the alimentary canal and in the kidneys. During their passage through the body they are generally diluted to such a degree that the irritation of other tissues is seen only when they are administered continuously. It may then lead to increased formation of fibrous tissue (arteriosclerosis and cirrhosis). Nephritis, however, often occurs acutely, and is produced by all absorbable irritants. The inflammation may involve all the renal tissues; or it may be glomerular or parenchymatous, according to the poison. Continued administration leads to intestitial nephritis.

The inflammation is characterized by albuminuria, casts, and the histologic lesions.

Experiments (Optional).— Rabbits can be conveniently used for the production of experimental nephritis. The presence of albumen, casts, and sugar should be sought for in the urine, and the kidneys should be hardened, stained, and examined histologically.

1. **Arsenic — Mainly Glomerules.**— Inject hypodermically 10 mg. per Kg. of potassium arsenate. The urine becomes albuminous in 10 minutes. The glomeruli are dilated, filling Bowman's capsule. The epithelium of the convoluted tubules is affected to a varying degree; the straight tubules are not involved.

2. **Aloin — Mainly Epithelium of Convoluted Tubules.**— Inject hypodermically 2 c. c. per Kg. of a 5% solution; repeat for two or three days. The action is practically limited to the convoluted tubules.

3. **Chromates — As Aloin.**—Inject hypodermically 30 mg. per Kg. of potassium bichromate; nephritis is plain in 24 hours.

4. **Cantharidin — All Renal Elements.**— Inject hypodermically 5 mg. per Kg. (dissolved in acetic ether). Albuminuria in 10 minutes.

5. **Mercuric Chlorid — Mainly Interstitial.**— Inject hypodermically 10 c. c. of 1 : 1,000 solution daily: Albuminuria in 2 to 3 days.

6. **Oxalates — Occlusion of Tubules by Crystals of Calcium Oxalate.**— Inject hypodermically 0.250 Gm. of ammonium oxalate into a rabbit.

Summarize the effects of Mercury in Chapter XXXVIII, No. 8.

EXERCISE 34.— GLYCOSURIA.

Study in connection with Chapter XIII.

Explanatory.— The presence of sugar in the urine may be due to several different causes. These are discussed in text-books of physiology.

The presence of reducing substance in the urine, after the administration of drugs, is often due to glycuronic acid, which is generally excreted in paired combination with the drug. These urines reduce Fehling's solution, but do not give the fermentation test.

The following are examples: Copaiba (Exercise 13, No. 6), Chloral, Menthol, Thymol, many volatile oils, Carbon-monoxid, Chloroform, Formates, free Oxalic Acid, Benzaldehyd, Morphin.

True glycosuria (in which the urine also gives the fermentation test) is caused by: Phlorrhizin, Adrenalin, Uranium, Curare, Cyanids, Atropin, Amyl Nitrite, Chromates and Bichromates, Mercury, Morphin, Cantharidin, extensive salt injections, etc.

Many of these act by producing asphyxia. Phlorrhizin acts directly on the kidney cells.

Experiments (To be distributed amongst the class).— **1. Phlorrhizin.**— (Renal action.)— Inject hypodermically into a rabbit 1/4 Gm. of phlorrhizin dissolved in 5 c. c. of warm water. Keep the animal in a cage arranged for the collection of urine. If none has been

Materials Required (for entire class).— 3 rabbits, hypodermic syringe, 25 c. c. graduate, catheter, test-tubes, etc., for sugar test. 1/4 Gm. phlorrhizin, 4% morphin salt (5 c. c.); Fehling's, or copper sulphate and NaOH for sugar test.

passed in an hour, withdraw by a catheter (see page 820), and demonstrate the presence of sugar by Fehling's or Trommer's tests.

2. **Morphin** (Asphyxial conversion of glycogen into glucose).— Inject hypodermically into a rabbit 2 to 3 c.c. of 4% morphin. Collect and test the urine as in Experiment 1. A respiratory tracing may be taken (see page 816) if the animal shows Cheyne-Stokes breathing (see Fig. 52, page 185).

3. **Adrenalin.**— Inject subcutaneously into a rabbit 1 to 2 c.c. of 1 : 1,000 adrenalin; in two hours, collect the urine and test as in Experiment 1.

Summarize the effects of Phlorrhizin in Chapter XXXVIII, No. 9.

EXERCISE 35.— METABOLISM.

Study in connection with Chapters IX and XVI.

Explanatory.— Drugs may alter metabolism directly, by acting on the tissues or on certain nervous centers; or indirectly, by influencing digestion, absorption, or excretion; or by making the animal quiet or restless, etc.

The experimental investigation of nitrogen or carbon metabolism entails extensive preparation and surveillance of the animals, and time-consuming analytic methods. The following experiments are therefore optional:

Experiments on Nitrogen Metabolism.— Dogs or rabbits may be used. Arrange for the regular collection of urine. The animals may be reduced to nitrogen equilibrium and then kept on a uniform diet; or they may be starved until the nitrogen is practically constant. The urine may be examined for total nitrogen and for urea. The following drugs may be tried:

Quinin: 0.05 per Kg.
Antipyrin: 0.02 Gm. per Kg.
Water: Large quantity.

The following drugs are important: Quinin diminishes nitrogen metabolism; the coal-tar antipyretics also, but only in fever. Morphin diminishes carbon metabolism. Phosphorus in toxic doses increases nitrogen metabolism, but diminishes urea. Acids increase ammonia excretion at the expense of urea; alkalies the reverse. Salts and water increase nitrogen excretion.

EXERCISE 36.— EFFECTS ON TEMPERATURE.

Study in connection with Chapters X and XVII.

Explanatory.— The temperature of an animal is determined by the relation of heat dissipation and heat production. The heat-regulating mechanism of warm-blooded animals is able to keep the temperature of the body constant, notwithstanding all ordinary variations of external and internal conditions. The temperature can therefore be altered only by very violent changes, or more commonly, by disturbing the regulating mechanism. Several centers are concerned in the latter. Successive stimulation or section of the paths is necessary to distinguish which of these is concerned in a given phenomenon. These experiments are rather complicated.

By the use of the calorimeter and by the study of metabolism it is

Material Required (for entire class).— Rabbits, thermometers, stomach tubes, and hypodermic syringes. (Rabbits 4 and 7 should receive the albumose four hours before the class meets.) 10% chloral hydrate (15 c.c.); 4% morphin salt (10 c.c.); 5% cocain salt (10 c.c.) 20% Witte's Peptone (15 c.c.); 5% sodium santoninate (30 c.c.); 2% antipyrin (50 c.c.).

easy to determine whether the change of temperature is due to altered heat production or heat loss. The plethysmograph will show whether changes in heat loss are due to an action on cutaneous vessels. The evaporation of sweat may be excluded by atropin, which paralyzes the sweat-glands.

The drugs which increase temperature act generally on heat production, by increasing muscular movement. Cocain acts on the centers of the caudate nuclei. The hypodermic injection of irritants, even of water, and especially of albumose, produces some hyperpyrexia in rabbits. Bacterial toxins are the most efficient pyretics.

The drugs which lower temperature may do so by producing a general depression of the central nervous system — a shock or collapse action. Alcohol, chloral, morphin, etc., belong to this class. These lower the temperature even in previously healthy individuals.

The typical antipyretics, on the other hand, lower the temperature only when it is abnormally high, *i. e.,* in fever; and then only to normal. The coal-tar antipyretics (acetanilid, antipyrin, etc.) act centrally, and increase the heat dissipation by dilating the cutaneous capillaries. Quinin diminishes the heat production by a direct action on the muscular metabolism.

Experiments (Optional).— **Observations Required.**— Rectal temperature (every half hour), (see page 820). The observations should be made before giving the drugs, and a normal animal should be kept and observed under perfectly uniform conditions, to exclude accidental variations. (The effects are usually seen in two to three hours.)

1. Chloral (Fall of temperature by collapse).— Give a rabbit 0.6 Gm. per Kg. of chloral (6 c. c. per Kg. of 10%) by the stomach-tube. There is a fall of temperature, general depression and partial or complete anesthesia. The respiration is slower and more shallow. (Depression of medullary centers.)

2. Morphin (Fall of temperature by diminution of metabolism, and perhaps by a specific effect on temperature centers).— Inject hypodermically 0.1 Gm. per Kg. (2.5 c. c. per Kg. of 4% solution). The effects resemble those of chloral, but are not so severe. (Test urine for sugar.) A respiratory tracing may be taken (see page 816) if the animal shows Cheyne-Stokes respiration (see Fig. 52, page 185).

3. Cocain (Rise of temperature through stimulation of the caudate nucleus).— Inject hypodermically 50 mg. per Kg. (1 c. c. per Kg. of 5%). Rise of temperature of 1 to 2° C.

4. Albumose (Rise of temperature).— Inject hypodermically 1 Gm. per Kg. (5 c. c. per Kg. of 20%): Rise.

5. Santonin (Fall, then rise).— Inject into the stomach 0.5 Gm. per Kg. of Santoninate of sodium (10 c. c. per Kg. of 5%): There is at first a fall of temperature, due to the increased heat loss. Convulsions set in, and when these are violent, the temperature may rise on account of the increased muscular activity. When the convulsions give place to paralysis, there is a second more profound fall of temperature. (Santonin illustrates typically the effect of all convulsant poisons on temperature.)

6. Antipyrin (Little effect on normal animals).— Give a rabbit 0.1 Gm., per Kg. (5 c. c. per Kg. of 2%) by the stomach-tube. There is little, if any, effect.

7. Antipyrin in Fever (Regulation of temperature).— Give the rabbit albumose, as in Experiment 4, and follow this in four hours by antipyrin (as in Experiment 6). The temperature soon returns to normal, whilst that of 4 remains high.

Summarize the effects of Antipyrin in Chapter XXXVIII, No. 10.

EXERCISE 37.—STIMULATION AND DEPRESSION (INTRODUCTION).

Study in connection with Chapter VII.

Pharmacologic agents act by increasing or diminishing the normal functions of the tissues. They never create new functions. Exceptions to this rule are few, and indeed, only apparent. They depend on the exaggeration of a function which is normally so slight as to be imperceptible; or which may be latent on account of unsuitable conditions.

An increase of function is called *stimulation*. If it is accompanied by inflammatory phenomena, it becomes an *irritation*, and is necessarily harmful to the tissue. A stimulation may be harmless, although it tends to pass into fatigue or exhaustion.

A diminution of function is termed *depression*. If the function is entirely abolished, we speak of *paralysis*. This permits of recovery, if it involves only one function. If all the functions are paralyzed, we have *death*.

The majority of drugs and poisons produce stimulation at first or in smaller doses; and depression in larger doses. The principal differences are found in the relative degree and duration of the stimulation and depression. A fairly large number of drugs, however, produce depression without preceding stimulation; in a few, the stimulation is not followed by depression. In a very few exceptional cases, a depression appears to precede a stimulation; but it is likely that this is merely apparent; for instance, it may depend on the involvement of different structures.

The *immediate and late effects* of the same drug, and the action of small and large doses, are therefore often opposed. As a general rule, the large doses produce at first the effects of small doses, even when they have the opposite effect later. It is customary to distinguish these successive actions as *primary and secondary* (and sometimes tertiary), or preferably, as *early* and *late* affects.

A critical analysis of the actions of of drugs shows them to be very simple in principle: The great majority produce a primary stimulation and secondary depression of most of the structures to which they may be applied. The details, however, present an infinite variety, according to the organs and functions which are most affected.

Most drugs have a *selective action*, in this sense. The detailed study of these selective actions constitutes the special aim of *pharmacodynamics*, and is of the greatest importance to the physician.

It is rarely possible to understand the actions of a drug by the observation of the symptoms which it produces. Special experiments are required, consisting essentially in the functional isolation of structures which might be involved. The following principles are generally applicable:

The structures which might be involved are considered in the direction of a reflex-chain (Fig. 44, page 121).

In case of stimulation, the links of this chain are successively paralyzed: The site of the stimulation is just central to the point at which paralysis abolished the action. The paralysis is accomplished by section or by drugs.

In case of paralysis, the links of the chain are successively stimulated: The site of the paralysis is just central to the point where stimulation is effective. The stimulation is made electrically or by drugs.

In the actual experiments, the structures are not taken in the order named, but according to convenience of technic. It is customary to start with the nerve trunk and then to work centrally or peripherally as the result may indicate.

EXERCISE 38.— STUDY OF THE LOCATION AND TYPE OF CONVULSIONS ON FROGS.

Study in connection with Chapter VIII.

Review electric stimulation, page 792 and 793; and administration, page 795.

Explanatory.— This exercise involves the application of the principles of the last lesson. Both strychnin and picrotoxin cause convulsions. The action might conceivably be located in the sensory endings, in the brain, medulla, spinal cord, motor endings, or muscle fibers. If it is central, it could be due to direct stimulation, or to increased sensibility to reflex impulses.

The student will determine the correct explanation by his experiments.

The type of the convulsions, when once seen, gives a very plain hint of the probable location of the action. The student should tabulate the distinctive differences between strychnin and picrotoxin. This will be facilitated by the use of the following terms:

Opisthotonus: Body arched backward.
Emprosthotonus: Body arched forward.
Clonic Convulsions: Intermittent, jerky.
Tetanic Convulsions: Permanent stiffening.

Quite a number of poisons produce the same effects as strychnin; for instance, small doses of caffein; morphin also produces the same action, after a time. (Consult Exercise 41, No. I.)

Large doses of caffein and veratrin also produce effects which resemble those of strychnin superficially (consult Exercise 45). The action of caffein, however, is due to rigor, for it persists after cutting the nerve, and the muscles are inexcitable. Veratrin acts directly on the muscle fiber, for even the isolated muscle remains contracted for a long time, whenever it is stimulated.

Experiments.— Half the set should work with strychnin (I), the other half with picrotoxin (II).

I. Strychnin (Increased reflex excitability of the spinal cord).— **1. Type of the Convulsions.**— Inject into the lymph sac of a frog ¼ c. c. of $^1/_{10}$% strychnin. Observe the type of the convulsions carefully. Note when they appear; that the legs are extended, and the arms flexed; the frog may be held horizontally by the feet. The convulsions intermit, the frog being paralytic between the spasms. The spasms may start with a cry. Make a written description of the effects, and draw a sketch of the typical tetanus.

2. Nature of the Stimulus.—(*a*) Note, on the above frog, that the convulsions appear, as a rule, only when the animal is stimulated. Note that the following stimuli are effective: touching, jarring the table, sound (clapping hands), electric stimulation of the skin.

(*b*) Pith the brain (see page 795) of the same frog (or of another poisoned by strychnin) and remove the skin from the muscle of one leg; expose the sciatic nerve (see page 796) of the same leg; expose the

Materials Required (for six students).— 8 frogs; 2 injection pipettes; hypodermic syringe and needle; dissecting apparatus; induction coil with fittings; 2 pithing needles. $^1/_{10}$% strychnin sulphate (5 c. c.); 1 : 250 aqueous picrotoxin (3 c. c.); $^1/_{100}$% strychnin sulphate (5 c. c.). (The last for demonstration.)

intestine. Determine the weakest current which will set off a spasm if applied to the skin of the intact leg. Try the same current on the exposed muscle, nerve, and intestine. Strengthen the current as necessary; an effect may be obtained, first from the nerve, then from the skin, then from the muscles, and last from the intestine. Formulate conclusions.

3. **Location of Tetanus.**— Inject ¼ cc. of $^1/_{10}$% Strychnin into a frog. (*a*) Immediately after the convulsions appear, divide the sciatic nerve of one leg; the leg does not participate in the convulsions. (*b*) Destroy the brain in the same frog; the convulsions continue. (*c*) Destroy the medulla in the same frog; the convulsions continue. (*d*) Ligate the leg of another frog, exclusive of the sciatic nerve. Inject ¼ c. c. of $^1/_{10}$% strychnin below the ligature; no convulsions. Formulate conclusions for Experiment 3.

4. (Demonstration.) Inject 0.4 mg. per 100 Gm. of strychnin sulphate (4 c. c. $^1/_{100}$% per 100 Gms.) into a frog. When the paralytic condition predominates, place on ice over night; the animal again becomes convulsive (the convulsions were obscured by the paralysis). (See also Baglioni's experiment and exclusion of posterior root ganglia, page 144; the technic is described in Edmunds and Cushny, page 75.)

II. Picrotoxin (Stimulation of the medullary centers).— Make the experiments as for strychnin (I, 1, 2*a*, 3*a*, *b*, *c*), using 1.5 c. c. of 1 : 250 solution.

1. The convulsions occur only after a period of depression lasting to half an hour. The animal goes through a regular cycle of motions; a characteristic feature is that the legs are abducted in one stage. The animal may turn a somersault. The abdomen may be bloated with air. Between the spasms the animal is paralyzed.

2. Note that the convulsions may occur in the absence of stimulation.

3. *a* and *b*, as in strychnin; *c*, the convulsions stop.

III. Optional.— Ammonium Carbonate 0.025 Gm.; Camphor (1 cc. of spirits) or Carbolic Acid (1 c. c. of 1%) may be used in place of picrotoxin, but the effects are less typical.

Summarize the effects of Picrotoxin in Chapter XXXVIII, No. 11.

EXERCISE 39.— CONVULSANTS, MAMMALS.

Study in connection with Chapters VIII, XV, XX, and XXI.

Explanatory.— The effects of convulsant poisons are very similar in frogs and in mammals. They can be localized by the same methods, but the technic is naturally more difficult in the higher animals. Only the symptoms will be studied in this exercise. The seat of the action is the same as in the frog.

Spinal Convulsants produce increased reflex excitability, and then tetanic opisthotanus. Strychnin is the principal example; caffein belongs to the same group.

Medullary Convulsants produce clonic spasms with tendency to emprosthotonus. Nicotin and hydrocyanic acid (consult Exercise 24, No. III) belong to this group. They act by producing asphyxia which is the direct cause of the convulsions. Veratrin, camphor, picrotoxin, cornutin, and some others act directly on the centers.

Cerebral Convulsants act on the motor areas. They produce rythmic twitchings of muscles (choreiform contractions) or epilepti-

Materials Required (for entire class).— 3 rabbits; bell jar; hypodermic syringe and needle; guinea pig. $^1/_{10}$% veratrin (5 c. c.); 20% camphor in oil (10 c. c.); coal gas.

form spasms. These are sometimes seen in morphin poisoning. They are also produced by absinth.

Psychic Excitants produce constant motion, but of a purposive type, plainly due to excitement. The movements may assume various types: There may be simply an increased vivacity, as with atropin (see Exercise 28, No. 1); or the animal may become maniacal, as sometimes with Cannabis (see Exercise 24, No. II); or it may run constantly in a circle.

The central action may also remain localized in certain *definite centers*. Small doses of caffein, for instance, cause an increase of psychic activity and tendency to wakefulness. Apomorphin acts mainly on the vomiting center; the antipyretics on the temperature. Drugs may also stimulate the vasomotor, vagus, or respiratory center, etc.

The action of convulsants on mammals is often not sharply localized, but involves different centers in succession, generally from the brain downward. Cocain, carbolic acid, and asphyxia are examples.

It will be noted, in the following experiments, that the stimulation is generally followed by depression.

Present the differences in the symptoms from spinal and medullary convulsants in tabular form.

Experiments (Demonstration).— **I. Strychnin** (Increased excitability of spinal cord). (Consult Exercise 24, No. 1, and Exercise 29. If these have been sufficiently illustrative, they need not be repeated.) Increased reflex excitability; sudden spasms; opisthotonus; intermissions with paralysis. Make a drawing of a typical convulsion.

II. Veratrin (Stimulation of Medulla).— Inject hypodermically into a rabbit 1 mg. per Kg. of Veratrin salt (1 c. c. per Kg. of $^1/_{10}$%). Repeat in 20 minutes, if necessary: salivation, incoordination, irregular convulsions, animal jumps straight up ("bucks"). Paralytic condition. If death should occur, the respiration stops before the heart. (The commercial samples of veratrin vary considerably in their activity and it may therefore be difficult to hit upon the proper dose which is required to produce the "bucking.")

III. Camphor (Stimulation of the Motor Areas and Medulla).— Administer 25 c. c. of a 20% solution of camphor in oil to a rabbit by stomach tube. The convulsions, which occur in about 30 minutes or later, resemble those of veratrin.

IV. Asphyxia (Mainly medullary stimulation).— Place a guinea pig under a bell-jar, and pass coal-gas under the jar; the animal gives signs of discomfort, goes into incoordinated convulsions, and then into coma. Remove the bell-jar, and start artificial respiration; prompt recovery.

EXERCISE 40.— CENTRAL DEPRESSANTS, MAMMALS.

Study in connection with Chapters IX and XIX.

Explanatory.— Central depressants may involve the same structures as the convulsants. The action, however, is not usually localized as sharply; especially when different doses are compared. The order in which the centers are paralyzed is generally: Brain, spinal cord, medulla.

Depression of the brain interferes in the first place with the higher psychic processes; this passes into sleep, and finally into anesthesia.

Materials Needed (for entire class).— 3 small dogs; 1 cat; 1 rabbit; 2 guinea pigs; 5 c. c. hypodermic syringe with large needle; stomach-catheter and bulb; rectal thermometer; measuring pipette; tumbler and cotton. 4% morphin sulphate (5 c. c.); ether (100 c. c.); chloral, 10% (15 c. c.); ethyl chlorid; 25% $MgSO_4$ (20 c. c.).

Depression of the spinal cord leads to loss of reflex excitability; depression of the medulla, to fall of blood pressure, quickening of the pulse, slowing of respiration, and fall of temperature. The location of the action of the depressants is therefore indicated by the symptoms.

The readiness with which the successive stages may be produced, and their duration, varies with each drug, and determines its uses in therapeutics.

Those which act mainly on the higher centers are used for the relief of pain (analgesics) or for producing sleep (hypnotics): Morphin, Cannabis, Alcohol, Chloral.

Those which act profoundly on the brain and spinal cord are employed for operative anesthesia (general anesthetics): Ether, Chloroform, Ethyl Chlorid, etc.

Paralysis of the medulla (Chloral, Chloroform) is only utilized in experimental technic; but it is important as a source of danger in anesthesia. It is treated mainly by artificial respiration.

It will be remembered that most central stimulants also produce some depression; similarly, the depressants often cause some stimulation. Morphin may produce excitement in certain individuals; it may also stimulate the vomiting and defecating and motor centers. It always increases the reflex excitability of the spinal cord, and may even cause typical strychnin spasms in the lower animals.

Alcohol and the general anesthetics produce a preliminary stimulation. This, however, is not due to a direct stimulant action, but to inhibition of restraining centers, and to reflex stimulation.

Experiments (To be distributed amongst the class):

Consult Exercise 24, No. II, Cannabis Indica.
" 29, " VI, Alcohol.
" 36, " I, Chloral.
" 36, " II, Morphin.
" 30, " 4, Morphin.
" 34, " 2, Morphin.
" 39, " IV, Asphyxia.

(If the chloral and morphin experiments have been sufficiently illustrative, they need not be repeated.)

I. Morphin.— (*a*) *Dog.*— Observe the pulse, respiration, temperature, reflexes, and pupils of a dog, taking care that the animal is not excited. Inject hypodermically 2 c. c. of 4% morphin and carefully observe the effects. The animal will probably vomit and pass feces and sometimes urine. (Stimulation of medullary and spinal centers?) The respiration may be temporarily quickened, but will soon become slowed and more shallow (stimulation and depression of the respiratory center). A tracing may be taken (see page 816 and Fig. 52, page 185). The pulse rate will decrease (stimulation of vagus center). The temperature falls (general lowering of metabolism). The pupils are variable (central action). The animal becomes more quiet; does not move spontaneously, and the movements are shivering. The hind legs are especially affected, and may be dragged when the animal walks. The dog does not usually fall asleep; but pain is felt less acutely. The reflexes, however, are not diminished.

The effect is on the whole a central depression; the action differs from that on man mainly by the absence of sleep, and by the presence of the diarrhea, by the variability of the pupils, and by the more pronounced motor disturbances.

(*b*) *Cat.*— Observe pupils, respiration, and pulse. Inject hypodermically 1 c. c. of 4% morphin. The effect is excitant, the animal running about. The pupils dilate.

(*c*) *Guinea Pig.*— Take the temperature and respiration. Inject hypodermically 1 c. c. of 4% morphin. The animal is depressed, and may perhaps die eventually; but death is preceded by convulsive shivering, which can be felt by suddenly lifting the animal.

II. Chloral.— Take the temperature and respiration of a rabbit. Inject into the stomach 0.6 Gm. per Kg. of Chloral (6 c. c. per Kg. of 10%) and note the effects. The rabbit becomes depressed; this may increase until the animal lies motionless on its side. Lift a leg and note that there is no muscular resistance; painful manipulations produce no effect. The respiration is slow and shallow (depression of the respiratory center). The temperature falls greatly (increased loss, and diminished production of heat, due to the general depression).

III. Ether (see page 803).— Take the pulse, respiration, and temperature of a dog; also note the pupils. Pour a tablespoonful of ether on a sponge or cotton, and apply to the mouth of the dog, covering the entire mouth closely with a folded towel. The dog must be held firmly between the knees. The animal at first struggles fiercely (first stage of anesthetia; due mainly to reflex irritation and to asphyxia). The struggles soon cease, the animal becomes quiet and falls on its side. Lift a leg and note that there is no muscular resistance. Painful impressions (pinching) produce no reaction. The conjunctival (winking) reflex usually persists until very late. The respiration is slowed and shallow. The temperature falls. The pupils are variable, but usually constricted. The pulse-rate is slowed. Withdraw the ether and note that the animal recovers consciousness rapidly, and that all the functions undergo improvement. Some degree of depression and motor-incoordination persists, and the animal remains nauseated and very thirsty for some time. The effects of the ether bear a close resemblance to that of chloral; but with chloral the struggling is absent, and the anesthesia more persistent.

IV. Ethyl Chlorid.— Put some cotton in a tumbler. Spray on this about a teaspoonful of ethyl chlorid. Invert over the mouth of a dog, wrap with a towel. Anesthesia occurs very promptly, and recovery follows as quickly when the tumbler is removed. The anesthesia is a mixed effect of the very quickly acting anesthetic, and of asphyxia.

V. Magnesium.— Inject hypodermically into a guinea pig 5 c. c. per Kg. of 25% $MgSO_4$ (or into a rabbit, 7 c. c. per Kg.): Complete anesthesia in an hour, followed by complete recovery.

EXERCISE 41.— CENTRAL DEPRESSANTS, FROGS.

Explanatory.— This exercise should be compared with Exercise 40. It will be seen that the phenomena are essentially similar. The successive, descending paralysis of the higher centers by morphin is much more sharply defined.

Each set of three students may take one of the experiments.

Experiments.— I. Descending Central Paralysis (Morphin).— Inject into the lymph sac of a frog 50 mg. of morphin sulphate (1¼ c. c. of 4%). Observe the symptoms (which correspond to the ablation of the central nervous system at successively descending levels). The

Materials Needed (for 12 students).— 4 frogs, morphinized frog; injected several hours before the exercise; frog board; 2 tumblers; induction coil; pipettes; cotton. 4% morphin solution (2 c. c.); 95% alcohol (2 c. c.); 10% chloral (2 c. c.); ether (10 c. .c); 25% $MgSO_4$ (5 c. c.).

animal at first becomes quiet, and does not move spontaneously; it sits erect, however, and jumps if stimulated. Place the animal on a small board, and tilt the head-end slowly up: the animal will climb up the board (if observed sufficiently early: later it will not do so). Laid on its back it recovers its normal position. Place the morphin frog and a normal frog in a tumbler filled with water, and invert this over a large jar filled with water (not admitting any air into the tumbler). Both frogs will rise to the top to breathe; but the normal frog finding no air, will dive down and out of the tumbler; the morphinized frog remains. Remove it from the tumbler and observe that it can swim. Remove from the water. As the action of the poison progresses, the frog will sit more flat. Laid on its back it makes ineffectual efforts to turn. Still later the frog lies quite flat, makes no effort to turn, and cannot swim. On pinching the toe, the leg still contracts. This shows that the cord and the peripheral sensory and motor nerves are not paralyzed. Lay the frog aside; in the course of some hours, or on the next day, the animal is found in typical strychnin convulsions. (One of the frogs may receive the morphin several hours beforehand, and the convulsions demonstrated.)

II. Alcohol.— Inject into the lymph-sac of a frog about 0.5 c. c. of alcohol (95%): Paralysis, abolition of reflexes, and respiration. Some preliminary excitement, due to local irritation.

III. Chloral.— Inject into lymph-sac of frog 1 c. c. of 10% chloral: Effects as with alcohol.

IV. Ether.— Place a frog under an inverted tumbler containing some cotton saturated with ether: Effects as with alcohol.

V. Magnesium.— Inject into lymph sac 0.8 c. c. of 25% $MgSO_4$ for each 10 Gm. of frog. Complete anesthesia in an hour. Recovery by next day.

EXERCISE 42.— PERIPHERAL MOTOR PARALYSIS, FROGS.

Study in connection with Curare, Chapter XII.

Explanatory.— To determine whether a motor paralysis is central or peripheral, the sciatic nerve is exposed and stimulated electrically. If there is no response, the paralysis is peripheral. If the muscle contracts, the central seat of the paralysis is located by successive stimulation of the cord and medulla.

A peripheral paralysis may be in the nerve-trunk, the endings, or the muscle fiber. No drug is known which acts selectively on the motor nerve-trunk when applied systemically. The possibility of this action may be excluded by the curare experiments described below. If the motor endings are paralyzed, the muscle will contract if the electrodes are laid directly upon it. This effect is produced most typically by curare; but it is also shared to a minor degree by strychnin, coniin, lobelin, camphor, organic ammoniums, etc. These drugs, however, have other actions, which are much more powerful, and which generally kill the animal in doses much smaller than those required to produce the curare effect. This may therefore be very incomplete, or may be demonstrable only by local application to frog's muscles.

Materials Needed (for 18 students).— 6 frogs; dissecting tools; 1 c. c. injecting pipettes (3); 2 capsules and slides; 6 induction-coils with batteries and electrodes. Demonstration.— Belljar, cigar, frog.

Solutions (all in normal saline).— ½% curare (5 c. c.); $^1/_{10}$% curare (20 c. c.); 0.2% nicotin (5 c. c.); 0.1% nicotin (20 c. c.); 0.1% physostigmin (10 c. c.); $^1/_{10}$% sapotoxin (10 c. c.).

Experiments.— One experiment may be assigned to each set of three students. For instance: Set A = I, 1 and 2; B = I, 3; C = I, 4 and 5; D = II, 1 and 2; E = II, 3; F = IV; III = Demonstration. If the curare experiment has been performed satisfactorily in the physiology course, No. I, 1 — 3, need not be repeated.

I. Paralysis of the Nerve Endings in Striped Muscle (Curare).

1. *General Symptoms.*— Inject ½ to 1 c. c. of a ½% solution of curare into the lymph-sac of a frog, repeating the dose every 20 minutes if necessary. Note the general symptoms; the reflexes disappear and the frog shows a general muscular paralysis, but without the preceeding cerebral depressions which was observed with morphin.[1]

2. *Seat of the Paralysis.*— When the reflexes have entirely disappeared in the above frog, isolate and stimulate a sciatic nerve (see page 796). There is no response (or if the poisoning is incomplete, only a slight contraction). The paralysis is therefore peripheral to the cord. Apply the electrodes directly to the muscle; there is a strong, normal contraction. The muscle fibers are therefore not paralyzed. The curare must therefore act either on the nerve-trunk, or on its endings.

3. *Seat of Paralysis, Continued* (Claude-Bernard's Experiment).— Take another frog, pith its brain, and ligate one leg, excluding the sciatic nerve. Inject the dose of curare used in (1) into the lymph-sac, and allow it to develop its action. Stimulate the sciatic nerve of both legs; the unligated leg does not respond, the ligated leg contracts. Direct stimulation of the muscle produces contraction in either leg. The ligature, which prevented the action of the curare, excluded the poison from the nerve endings, but not from the greater part of the nerve-trunk. It follows that the curare paralyzes exclusively the (motor) nerve endings.

4. *Seat of Paralysis, Continued.*— The conclusions of 2 and 3 may be arrived at more simply, and on one animal, as follows: Fit a slide across a small evaporating dish containing some 1/10% curare solution in normal saline; the solution should not reach the slide. Make two muscle-nerve preparations (see page 797) from a fresh frog, determine the smallest current (see page 799) which will give contraction when applied to the nerve, and directly to the muscle. Lay the muscle of one preparation on the slide, letting the nerve dip in the solution. Lay the nerve of the other preparation on the slide, letting the muscle lay in the solution. Remove the preparations every five minutes, testing their excitability as described above; replace them, and repeat as often as necessary. Present the results in tabular form:

STIMULATION OF:	NERVE IN SOLUTION.		MUSCLE IN SOLUTION.	
Distance of coils:	MUSCLE.	NERVE.	MUSCLE.	NERVE.
Before laying in solution..	......	......	......	......
5 minutes................	......	.....	......	......
10 minutes................	......	......	......	......
Etc.	......	......	......	......

The nerve which has lain in the curare retains its its excitability. The preparation of which the muscle has lain in the solution becomes inexcitable to stimulation by the nerve; the muscle itself retains its excitability. The action of the curare must therefore be on some structure between the nerve-trunk and the muscle fiber.

5. *Antagonistic Action of Physostigmin.*— Lay the curarized muscle of the last experiment in 1 : 1,000 Physostigmin (in normal saline).

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[1] With some samples of curare, strychnin tetanus precedes the paralysis.

Test the excitability from time to time: Some recovery occurs, the physostigmin removing the curare block.

II. Partial Curare Action and General Depression (Nicotin).

1. Inject into the lymph-sac of a frog 2 mg. (=1 c.c. of 0.2%) nicotin. Note that the frog becomes gradually depressed, assuming the characteristic positions illustrated in Fig. 61, page 263. (Note the peculiar twitching of the muscles. Divide one sciatic nerve; the twitchings cease. Stimulate the nerve; they reappear. The seat of this action is therefore in the muscle or endings, but it can only find expression if the nerve is stimulated from the brain or electrically.)

2. Make a muscle-nerve preparation from the frog, and test the quantity of current required (*i. e.,* the distance of the coils) to obtain a contraction if the electrodes are applied to the nerve, and if they are placed directly on the muscle; less current is needed on the muscle. Since the reverse is the case in a normal preparation, it is evident that the nicotin must have depressed the nerve-trunk or the endings.

3. Test the effect of 1:1,000 nicotin on the excitability of muscle and nerve, as in No. I, 4. It will be seen that the drug depresses first the endings, then the muscle, then the nerve-trunk.

4. (Optional.) The following drugs may be used in place of nicotin:

	IN LYMPH-SAC.	LOCALLY (in 0.75 saline)
Camphor	0.1 Gm.	Saturated
Lobelia	2 Gm.	4%
Conium	2 Gm.	4%
Coniin	10 mg.	0.2%
Lobelin	10 mg.	0.2%
Strychnin	......	1%

III. Nicotin in Smoke (Demonstration).

Take a small tubulated bell-jar fitted with a doubly perforated stopper. One of the perforations bears a tube reaching just below the stopper. Into the other opening of the cork fit the drawn-out end of a wide glass tube. This end should reach to near the bottom of the jar. In the other end of this tube fit air-tight a cigar, with the end cut off. Place a frog under the bell-jar; fix the latter with vaseline on a glass plate. Light the cigar, invert a bottomless test-tube over it, and blow the smoke into the jar. The frog will show the same symptoms as in II, 1, since the nicotin is the main active ingredient of tobacco smoke.

IV. Paralysis of the Muscle (Sapotoxin).

Test the excitability of any muscle of a frog (see page 799) (direct stimulation); place it in a 1/10% solution of crude saponin in 0.75% NaCl, and note loss of excitability from time to time.

Other protoplasmic poisons also paralyze the muscle cells directly; *e. g.,* cocain or quinin (1 : 1,000 to 1 : 100 solutions). Apomorphin and copper salts have the same effect, even when injected systemically.

Summarize the effects of Sapotoxin in Chapter XXXVIII, No. 12.

EXERCISE 43.—PERIPHERAL SENSORY PARALYSIS.

Study in connection with Chapter X.

Explanatory.—Sensory paralysis is evidenced by failure to respond to sensory stimuli (motor paralysis having been excluded by stimulation of the sciatic nerve). Central paralysis is excluded by stimulation of an afferent nerve-trunk. If this proves effective, the sensory paralysis is peripheral. This may involve the nerve fibers, endings, or sensory end cells. It is not always possible to distinguish absolutely between these. Nerve-trunks are only paralyzed by direct application. As a general rule, this paralyzes both sensory and motor fibers, but the sensory fibers are affected much more readily. It is somewhat easier, however, to demonstrate the paralysis of the motor functions, as in the experiments below.

Sensory depressants are utilized for local anesthesia. General anesthesia may be produced by injecting them into the subdural canal. It must be remembered that they need to be brought into direct contact with the structure to be paralyzed. They are quite inactive on surfaces from which they are not absorbed, such as the intact mammalian skin. On the other hand, they are effective on mucous membranes and the frog's skin. In other situations they are used by hypodermic injection or painted on the nerve, or injected under its sheath. Cocain and its substitutes are the best examples of local anesthetics.

None of the peripheral sensory depressants are sufficiently selective to act from the circulation without producing general intoxication. They are therefore used locally, and in the case of local anesthetics the action is further confined to the place of application by restricting the circulation with a bandage or by suprarenal alkaloid.

Sensory anesthesia may also be produced by very powerful sensory stimulation. Most irritants are succeeded by anesthesia. Aconite and menthol are examples.

Experiments.— Consult the action of cocain in the eye: Exercise 27, No. 3; and Exercise 54. Each set of students should do Nos. I, II, and V *a*. Nos. III, IV *a, b,* and *c,* and V *b,* may be distributed amongst the sets.

I. Anesthetic Action on the Tongue.— Place the drug on the tip of tongue (or saturate a small piece of filter paper with the solution and place on tongue) and test the sensibility to touch. Use one of the following: (*a*) Cocain, a drop of 1%; (*b*) Eucain,[1] drop of 1%; (*c*) Yohimbin (chew 5 mg. tablet); (*d*) Aconite (drop of 10% tincture). In the last, the anesthesia is preceded by prickling.

II. Paralysis of Taste Endings.— (*a*) (*Specific.— Yerba Santo*).— Note the difference in taste of a plain $^1/_{10}$% solution of quinin hydrochlorid, and the same solution after the addition of 10% of fluid-extract of Yerba Santa.

(*b*) (*General.— Cocain.*) — Place a drop of 1% cocain on the tongue; after a few minutes apply a drop of the quinin solution; no taste.

(*c*) (*By Over-stimulation.— Strychnin.*) — Place a few drops of $^1/_{100}$% strychnin on the tongue, and then a little 10% sugar solution: no sweet taste.

III. Paralysis of Sensory Nerve Endings (Cocain, Frog's Foot).— Dip the foot of a frog into a 1% cocain solution. Compare the excitability of this foot (electric stimulation, pinching, 0.1% HCl, etc.) with the normal foot from time to time. The reflex (and sensation) will be completely lost inside of 10 minutes.

IV. Paralysis of Nerve-Fibers by Direct Application.— Make two

Materials Needed (for 12 students).— 3 frogs; dissecting tools; 3 induction coils; filter-scrap; 3 camel's hair brushes. 1% eucain (5 c.c.); yohimbin tablets; 10% aconite (5 c.c.); 0.1% quinin hydrochlorid (10 c.c.); same in 10% F. E. Yerba Santa (10 c.c.); 1% cocain (10 c.c.); 5% (5 c.c.); $^1/_{100}$% strychnin (10 c.c.); 10% cane sugar (25 c.c.); 2% HCN (5 c.c.); ethyl chlorid tube; 25% $MgSO_4$ (5 c.c.).

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[1] Or any of the cocain substitutes may be used.

muscle-nerve preparations (page 797); test the excitability of the nerve. Then paint on one (*a*) a 5% solution of *cocain*, on the other (*b*) 2% *hydrocyanic acid;* note that the excitability diminishes and disappears. Wash the nerve in normal saline; the excitability returns (*c*); do the same experiment with 25% $MgSO_4$. (This experiment may also be tried with ether; or the nerve may be exposed to CO_2 in a gas chamber; it can also be demonstrated that morphin has no effect.)

(*d*) (*Optional Experiment.*) *The fact that ether depresses the conductivity as well as the excitability* of the nerve can be demonstrated by arranging the sciatic nerve of a muscle-nerve preparation in a small gas chamber on two pairs of electrodes, which are applied to the proximal and distal extremities, of the nerve. On conducting ether vapors into the chamber, the excitability disappears first at the end of the nerve which is farthest removed from the muscle.

V. Freezing.—(*a*) Spray some ethyl chlorid on the back of the hand: This produces pain and then anesthesia. (*b*) Decapitate a pithed frog and trim away the viscera, so as to expose the sciatic plexuses. Expose the sciatic nerve of one thigh (page 796), without cutting or injuring it, and support it on a match-stick. Lay the frog with the ventral surface upward, arrange electrodes on the plexuses, and see that a weak stimulation is effective (flexing the knee before stimulating). Freeze the exposed sciatic by a spray of ethyl chlorid. The leg will make some spontaneous contraction during the freezing, but in a short time it will cease to respond to the electric stimulation of the plexus, the conductivity of the nerve being paralyzed. Remove the spray and melt the nerve by the heat of the finger: the stimulation again becomes effective after a time.

EXERCISE 44.—PROTOPLASMIC DEPRESSANTS.

Study in connection with Chapter VII.

Explanatory.—These paralyze nervous and muscular structures, but differ from the muscle-nerve poisons by acting also on monocellular organisms, and often even on ferments. These actions were studied in Exercises 19 B and 20. They can also be observed conveniently on ciliated cells and on vegetable seeds.

Experiments:

I. Paralysis of Cilia (To be assigned to a few sets).—(*a*) Cut off the lower jaw of one of the frogs used in a former experiment, so as to expose the ciliated mucosa of the pharynx and œsophagus. Irrigate with normal saline solution. Determine the time which a small bit of cork requires to travel a certain distance (which may be marked off by pin-pricks). Take a number of observations. Irrigate with the ether solution, and after a few minutes repeat the observations. It will be found that the ciliary movement is greatly slowed or arrested. If the cilia have not been too profoundly injured, they may recover if they are thoroughly washed with normal saline solution.

(*b*) The ether may also be administered in vapor form, by supporting the œsophagus on a small stand in a tumbler, which contains a little cotton saturated with ether, and which is covered by a glass plate.

II. Germination of Seeds (*Optional*).—"Arrange two 8-ounce wide mouth bottles with stoppers fitted with glass tubes, letting one tube extend to near the bottom of the bottle. Suspend in each, by means of cotton, a dozen seeds—corn, wheat, clover, beans, etc.—and intro-

Materials Needed.—2 frogs; dissecting tools; pipette; tumbler; glass plate; cork; normal saline saturated with ether; ether; cotton.

duce just enough water to maintain a saturated vapor. Set both bottles in a window. Through one pass *ether vapor,* through the other *air,* twice a day for a week. The seeds in both will swell from the absorption of water, but only the bottle with pure air introduced will grow. Reverse the two. The sprouting grain will have its growth checked and the etherized seeds will begin to grow."—(C. W. Greene.)

EXERCISE 45.—THE EFFECTS OF DRUGS ON STRIPED MUSCLE.

Study in connection with Chapters VIII, XV, and XVI.

Review the technic, pages 796 to 799.

Explanatory.—The actions of drugs on striped muscle are scarcely utilized in therapeutics, but they help to explain the effects on the cardiac muscle, which are very important. They are also of considerable scientific interest. The effects may involve the form of the contraction curve, its height, the rapidity of contraction or of relaxation, the load which the muscle can lift, the total work which it can perform, the promptness of fatigue, the minimal effective stimulus, the latent period, the rate of stimulation required for fatigue, etc. As a general rule, these functions are all affected in the same sense.

The majority of muscle poisons may be arranged in three groups, which are illustrated typically by caffein, quinin, and veratrin.

Caffein increases the activity of the muscle, in small doses; larger doses produce phenomena analogous to fatigue. Very large doses throw the muscle into rigor. The methyl-xanthins (caffein, theobromin, etc.) are the only typical representatives of this group.

Quinin depresses the muscle, and finally paralyzes it, without producing rigor. Only the smallest doses are somewhat stimulant. All protoplasmic poisons and apomorphin and potassium, calcium, and metallic salts produce these effects.

Veratrin causes the muscle to remain contracted for a considerable time, the curve resembling somewhat that of tetanus. It can be distinguished from this by the secondary contraction (see Experiment No. I, 3*e*); it is, however, an active contraction, for the muscle can sustain a weight. The effect is lessened by all agents which depress the muscle. A careful inspection of most veratrin tracings will show indications of two contractions, the first of which (Fig. 71 *a,* page 326) is short and fuses into the second (Fig. 71 *b,* page 116), persistent contraction. According to Bottazzi's Theory, all muscle contains two contractile elements, the rapidly contracting fibrillary substance and the slowly contracting sarcoplasmic substance. The former is much more excitable, and predominates so greatly in the skeletal muscle that it is alone represented in the ordinary contraction curve. It is acted on by caffein. Veratrin stimulates the sarcoplasmic substance so that it also participates in the contraction, and this explains the prolonged contraction, the second portion of the curve. The sarcoplasmic substance predominates in smooth muscle, so that its contraction is normally of the veratrin type; but it is further exaggerated

Materials Needed (for 12 students).—6 frogs; pipette; 4 muscle-levers and 10 Gm. weights; 2 maximal-load springs; 4 induction coils arranged for single break shock; 4 drums, fast and slow speeds; thread ligatures; dissecting tools; thermometer; ice; water bath; 4 short test-tubes. 0.75 NaCl (400 c. c.). The following drugs are all dissolved in this saline solution; 25 c. c. of each are required: Caffein, 1 : 100, 1 : 1,000, 1 : 10,000; quinin hydrochlorid, 1 : 100, 1 : 1,000, 1 : 10,000; KCl, 1 : 10,000; 1 c. c. of $^1/_{10}$% veratrin.

by veratrin. Digitalis and similar drugs belong to the same group. When these drugs act on the heart, they increase its tone, *i. e.*, they tend to increase the systole at the expense of the diastole. In the frog's heart they may even cause systolic standstill.

In studying the effects of drugs on skeletal muscle, they may either be injected into the lymph-sac, or the muscle may be laid into a solution of the drug in normal saline. Special conditions determine which of these methods is to be preferred. When the muscle is laid in the solution, the drug is not always rapidly absorbed. It may therefore happen that one muscle will be scarcely affected by a strong solution, whilst a weak solution may produce severe effects in another preparation.— All the muscular poisons act equally well after curare, showing that their action is indeed exerted directly on the muscle cells.

(Copies of the tracings should be inserted in the note-books.)

Experiments.— These may be distributed as follows:

Set A = II 2 and I 1; B = II 1 and I 2; C = IV *a* and I, 3 *a, e, b;* D = I, 3 *a, c, d,* and IV *b.*

I. Form of Curve.— 1. *Caffein.*— (*a*) Adjust a muscle lever with 10 Gm. weight to a smoked drum (fastest speed). Arrange an induction coil for single **break** shocks (see page 792). Excise a gastrocnemius muscle, with a bit of femur and Tendo Achilles attached (see page 797). Connect it with the muscle lever. Pass fine wire electrodes from the secondary through the muscle. Make a tracing of a single muscular twitch. (*b*) Lay the muscle for 5 minutes in 1 : 10,000 Caffein (without disturbing the apparatus if possible). Make another tracing. Repeat on the same muscle with 1 : 1,000 and 1 : 100 Caffein (Fig. 49, page 164). The more dilute solutions cause a higher contraction, with little change in the form of the curve. Stronger solutions produce a lengthening of the relaxations. The curve then becomes lower, the contraction is slower, and with the strongest solution the muscle does not contract at all. With fairly strong solutions the relaxations may show a series of waves, which are not yet satisfactorily explained.

2. *Quinin.*—(*a*) As in I (see Fig. 74, page 332).

(*b*) Use 1 : 10,000, and 1 : 1,000 and 1 : 100, each for five minutes. The weakest solutions may increase the height of contraction somewhat; but even fairly weak solutions lower the contraction, and finally paralyze the muscle completely (Cocain, apomorphin, potassium, or calcium, etc., may be substituted for the quinin, but they are less typical; Fig. 65, page 306).

3. *Veratrin.*— (*a*) Arrange the apparatus as in 1, *a* (a fairly slow drum may be used). Inject into the lymph-sac of a frog ¼ mg. of veratrin (¼ c. c. of $^1/_{10}$%). As soon as the symptoms are pronounced (so that the animal cannot draw up the legs for some moments after making a jump) pith the frog, and make the muscle-nerve preparations. Connect one muscle with the lever and electrodes (without removing the skin). Make a tracing. Observe that the heights and rapidity of contraction are about normal, but that the relaxation is greatly prolonged (Fig. 71, page 326).

(*b*) *Effect of Heat and Cold.*— Lay the muscle for five minutes in normal saline at about 5° C. Make another tracing. Repeat with saline at 10°, 20°, 30°, and 35° C. (Fig. 68, page 324). The lower temperature lessens the contracture; 20° and 30° prolong it; 35° lessens it. (If the veratrin action is only slight, the contracture may appear increased by cold, for this prolongs the relaxation in unpoisoned muscle.)

(*c*) *KCl after Veratrin.*— Remove the skin from a good veratrin muscle. Take a tracing. Drop $^1/_{100}$% KCl on the muscle, with a pipette, and take tracing from time to time; the relaxation is shortened (Fig. 70, page 325).

(*d*) *Fatigue.*— Take a tracing from a good veratrin muscle. Stop the drum and send a tetanizing current through the muscle for a short time (without taking a tracing); again make a tracing with a single break shock: The contraction will be found greatly shortened (Fig. 69, page 325).

(*e*) *Secondary Contraction.*— Make a muscle-nerve preparation from a normal frog. Lay the nerve of this on a good veratrin preparation, so that the cut surface lies on the tendon, and the long surface of the belly of the veratrin muscle. The nerve should be raised between the two points of contact by a match-stick. Stimulate the nerve of the veratrin muscle with a single break shock: The current of action will stimulate the normal muscle, so that it will also contract; but the contraction will be short, whereas the contraction of the veratrin muscle is prolonged. This shows that the veratrin contraction is not a tetanus; for if it were, the normal muscle would also remain contracted. Convince yourself of this by stimulating the nerve of the veratrin muscle with the tetanizing current: The normal muscle now remains contracted.

II. Maximal Load.— 1. *Caffein.*— Make two muscle preparations. Determine the lifting power, as described on page 799, first on the normal muscle, then after laying the one muscle in saline, the other in 1 : 10,000 caffein, for five minutes; again lay the one muscle in saline, the other in 1 : 1,000 caffein. The weaker caffein solution should increase the lifting power, the stronger solution should diminish it (as compared with the saline muscle).

2. *Quinin.*— Substitute quinin for caffein in the preceding experiment. The lifting power is decreased.

III. Fatigue (*Optional*).— Make two muscle preparations. Lay one in normal saline, the other in 1 : 10,000 quinin (for 5 or 10 minutes). Adjust two levers on a slow drum and connect with the muscles, using 10 Gm. weights. Arrange the induction coil for tetanus, passing the same current, by fine wires, through both muscles. Set off the drum, close the current, and obtain a tetanus tracing from both muscles, until they are fatigued. The quinin muscle should fatigue more rapidly. (Low concentrations of caffein would lessen the fatigue.)

IV. Caffein Rigor.— 1. *In Intact Frog.*— Inject into the lymph-sac of a frog 5 mg. of caffein (½ c. c. of 1%). The frog soon becomes rigid. Note the position which the frog assumes. Make a sketch. The muscles respond but feebly, if at all, to electric stimulation. Their reaction is acid to litmus. (With some species of frogs this rigor is preceded by convulsions of the strychnin type.)

2. *Muscle Tracing.*— Arrange a muscle on a lever, so that it may be dipped into solution without removing it from the drum. The lever should write very easily. Start the drum at the slowest speed. Raise a beaker containing 1% caffein, so as to immerse the muscle. This will be seen to shorten.

Explanatory.—This is an instance of toxic rigor, due presumably to coagulation of the muscle substance. It will be seen in the next exercise that water has the same effect. This rigor may also be produced in mammals, by the direct injection of caffein, chloroform, etc. It will be recalled that convulsant poisons, such as strychnin, hasten the onset of rigor, but this rigor mortis is probably distinct from the toxic rigor studied in this experiment.

V. Action of Drugs on Fatigue, in Man (*Optional*).— This may be studied by the spring ergograph. A normal tracing is taken and this is repeated in half-hour intervals after taking 0.3 Gm. of caffein or 20 to 40 c. c. of 20% alcohol. Some practice is required before reliable results can be obtained.

EXERCISE 46.—SALT AND ION ACTION ON MUSCLE AND NERVE.

Study in connection with Chapter XXIV.

Explanatory.—The physical effects of **osmosis** were studied in Exercise 23. It was shown that they cause alterations of the water and salt content of the cells. This results in irritation and eventually in depression. These effects can be observed in all tissues which are exposed to osmotic change; but they can be studied most conveniently in muscle and nerve.

The experiments of this chapter will demonstrate that even equiosmotic solutions are not indifferent to the tissues. This is partly explained by differences in permeability, equimolecular solutions being often anisotonic. But the entire exclusion of the osmotic factor still leaves a certain residuum of action. For instance, no cell can live for any length of time in a solution of a single salt, no matter what its concentration. Salts therefore have a specific toxicity, referable to their peculiar ions. This is distinguished as ion-action. This toxicity is lessened when other salts are introduced; very small proportions are often sufficient for this purpose. Whenever these proportions are altered, the functions are also changed; the ratio of ions to each other being of greater importance than their absolute quantity. The cathions appear to be more important than the anions. Vertebrate tissues require the presence of Na, K, and Ca. An excess of the last two ions becomes promptly depressant and toxic.

Isotonic solutions of non-electrolytes are much less toxic than electrolytes. The effects of the latter possess many features in common. They have been shown to vary directly with the electrical condition of the ions. These facts suggest that the ion-action can be referred in part to the electric charges or electrons which stimulate or depress in the same manner as other forms of electricity. This may be termed *electron-action*.

Physical experiments lead to the conclusion that these charges may be transferred to the particles in colloid solutions, thereby modifying the fluidity. This would also hold true of protoplasm, which may be considered a typical colloid solution. Osmosis accomplishes the same result by changing the water-content. These alterations of fluidity are probably the basis of the physiologic effects, both in osmotic and in ion action.

Experiments (Demonstration or assigned).—**I. Effect of Water on Muscle).**—1. *Excitability.*—Use the arrangement of Exercise 42, No. I, and make two muscle-nerve preparations. Immerse the nerve of one and the muscle of the other in tap water, and observe the loss of excitability from time to time.

2. *Water Rigor.*—Suspend a thin strip of muscle (the sartorius) of the above frog so that half of it dips into water: this will be seen to become thicker and shorter.

3. *Perfusion with Water* (Optional).—Divide one sciatic plexus of

Materials Needed (for entire class).—7 frogs; four watch glasses; capsule and slide; induction coil; rabbit and instruments for V; water bath with solutions; muscle-lever; slow drum. 10% NaCl (25 c. c.); 0.75% NaCl (25 c. c.); Ringer's Fluid (25 c. c.); 2% NaCl (25 c. c.); distilled water; solutions for experiment III, and for peristalsis experiment.

a frog and perfuse the vessels (see page 801) with distilled water. In a short time the muscles will show fibrillary twitchings and these will be succeeded by general convulsions. Since the legs participate (the nerves being divided), the action must be directly on the muscles. These will be seen to swell. Eventually they become paralyzed.

II. Hypertonic Solution on Nerve.— Arrange a muscle-nerve preparation on a lever, writing on a slow drum. Let the nerve dip into 10% NaCl solution. The muscle will execute a series of contractions, then remain in tetanus, and finally go into paralysis.

III. Rhythmic Contractions (*Functions of Ions*) (*Optional*).— 1. (*a*) Lay a frog's muscle in 100 c. c. of $^{m}/_{8}$[1] sodium acetate (1.7% of the crystals). Rythmic contractions appear after ten minutes to an hour. When these are seen add:

(*b*) 3 c. c. of m $CaCl_2$ (11%). The contractions disappear at once. Add:

(*c*) 9 c. c. of m sodium citrate (71% crystals). The contractions reappear.

Explanatory.— The predominance of one kind of ions (*e. g.*, sodium acetate) brings out the latent rhythmic property of the muscle. Automatic rhythmic contraction is therefore not confined to the cardiac muscle.

(*b*) The addition of a bivalent cathion (Ca) restores the equilibrium of the ions, and the condition returns to normal.

(*c*) The addition of the citrate inactivates the Ca, so that the sod. acetate ions again predominate, and the rhythmic contractions reappear.

2. Repeat 1, *a*. (*b*) Add 5 c. c. of m $BaCl_2$ (21%): The contractions become stronger. (Not all bivalent ions can take the place of Ca.)

3. Lay a muscle into a 0.43% solution of sodium fluorid (isotonic with 0.6% NaCl). Rhythmic twitches appear at once (the fluorid precipitating the restraining calcium); they disappear again in about 30 minutes (paralysis).

IV. Vitality of Tissues Influenced by Salt Action and Ions.— Excise the hearts of four frogs and place them in watch glasses containing (*a*) tap water; (*b*) 0.75% NaCl made with distilled water; (*c*) Ringer's Fluid; (*d*) 2% NaCl. Note the time which they continue to beat (*d* will stop first, then *a*, then *b*, then *c*).

Explanatory.— (*a*) and (*d*) will stop the heart by salt action since their osmotic pressure is unsuited to the tissues. (*b*) will continue longer since it has the proper osmotic pressure but will also stop because it has only one set of ions. (*c*) contains the proper ratio of ions, and the heart will finally stop mainly from the want of nutriment.

V. Effect of Salts and Ions on Peristalsis.— Set up a large water bath, regulated for 38° C., and containing a liter beaker of Locke's Fluid (this will be called the "stock solution"), and jars or beakers with 50 to 100 c. c. of the following solutions of the salts dried at 110° C. (which have about the same freezing point as 0.9 NaCl solution, to eliminate osmotic phenomena): 0.9% NaCl; Na_2SO_4, 1.9%; $CaCl_2$, 0.15%[2] in 0.9% NaCl; $BaCl_2$,[2] 0.24% in 0.9% NaCl; $MgCl_2$,[2] 0.19% in 0.9% NaCl; Urea, 1.9%; also water, and 2% NaCl. Pass a slow stream of oxygen through the stock solution, and for a few minutes through each of the other solutions just before using.

Administer chloral to a rabbit (0.6 Gm. × Kg., stomach). Open the abdomen by a free incision. Insert a cannula into the central end of the abdominal aorta. Bleed the animal to death, defibrinate the blood, and pour this into the stock-beaker of Locke's Fluid. Excise the whole intestinal tract, except the cæcum, and place it into the blood mixture in the water bath. Note that it continues to perform peristaltic movements (for hours). Pinch a place with forceps and notice the contraction. Cut off a piece about 10 c. m. long, and place it in the 0.9% *NcCl* solution. Note the vermicular movement (which becomes weaker in time, but continues over 45 minutes). Most other sodium salts will have a similar effect, the cathartic salts (*citrate, sulphate,* etc.) being rather more powerful. Transfer the piece of intestine to the *calcium* solution: the movement stops and the intestine relaxes; the peristalsis reappears when replaced in the NaCl. Transfer another piece (from the stock-beaker) into the *magnesium* solution. The movement stops. On replacing the calcium and magnesium specimens in the stock solution, the movements resume.

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[1] A molecular or "m" solution contains the molecular weight of the substance, expressed in grams, dissolved in a liter of water.

[2] This corresponds to $^{1}/_{10}$ the isotonic quantity of the salt.

These experiments illustrate the antagonism of sodium salts on the one hand, and calcium and magnesium on the other. This stimulant effect of the sodium salts is doubtless concerned in their cathartic action. But the experiment with magnesium shows that it is not the only factor; for magnesium salts, administered by the mouth, are active cathartics.

The effects of barium are peculiar: Place a piece of intestine into the barium solution: after a few vermicular movements, it undergoes a firm tetanic contracture. Peristalsis reappears when the intestine is replaced in the Locke's Fluid.

Place other pieces of intestine into the *urea* solution, the water, and the 2% NaCl. They make vermicular movements or undergo tetanic contraction and then relax. Peristalsis is resumed in Locke's Fluid. These effects are due to osmosis.

Tracings may be taken from the pieces of intestine by attaching them to muscle-levers, leaving the tissue submersed in the fluid. The action of other drugs may be studied in the same manner (Magnus, 1905).

EXERCISE 47.— THE LOCALIZATION OF ACTIONS ON THE REFLEXES IN FROGS—(RECAPITULATION).

REACTION TIME.

This is measured as described on page 795 (see Fig. 44, page 121).

I. The Reaction Time is Shortened.— This may be due to—

(A) Increased reflex excitability of the cord — occurs after section of medulla.

(Strychnin, Caffein, etc.)

(B) Lessening of higher inhibition — does not occur after section of the medulla.

II. The reaction time is slowed or all reaction is abolished —

(A) No matter where the stimulus is applied:

1. *Depression of the Reflex Activity of the Cord.*— Stimulation of sciatic causes contraction.

(Carbolic Acid, Camphor in frog, and most depressant poisons.)

2. *Curare Action.*— Stimulation of the nerve is less effective than stimulation of the muscle.

(Curare-Nicotin series.)

3. *Paralysis of Muscle.*— Direct stimulation of the muscle is ineffective. The muscle may be:

(*a*) *Paralyzed:* it is soft and usually has an alkaline reaction.

(Copper — very strong doses of most drugs.)

(*b*) *In Rigor:* it is hard and has an acid reaction.

(Caffein.)

(B) The reflexes are diminished **only from those parts which have been touched** by the drug. There is a paralysis of the afferent nerves. This may be in:

1. *The nerve fibers:* Obtained best on subcutaneous injection and lasts long.

(Sapotoxin.)

2. *The nerve endings:* Equally well on painting on the surface; short.

(Cocain.)

III. The frog keeps the part to which the poison has been applied **in constant movement:** local sensory irritation, pain.

(Acids.)

FROG'S MUSCLE-NERVE CHAIN.

The intact animal shows:

I. Motor Paralysis.—This may be:

(A) Central.—Stimulation of the nerve is still effective. The seat may be in:

1. *The Brain:* The reflexes are still active. The phenomena produced by paralysis at different levels are given under Morphin, Exercise 41, No. I.

(Early stages of all narcotics.)

2. *The Cord:* No reflexes.

(Camphor, Quinin, Carbolic, Cocain, etc.)

(B) Peripheral.—Stimulation of the nerve-trunk has no effects. The paralysis may be in the endings or muscle, see page —, II, A.

II. Motor Stimulation.—This may be:

(A) Central.—Abolished by successive destruction of the central nervous system. The exact location may in this way be noted. It should be recorded whether the convulsions are idiopathic or reflex.

(Medulla = Picrotoxin; Cord = Strychnin, Caffein; Brain = Atropin, Cocain.)

(B) Peripheral.—Not abolished by section of the nerve; usually consists in twitching or increased force or lengthened time of contraction. It may be in:

1. *The Endings:* Abolished by Curare.

(Nicotin, Aconitin, etc.)

2. *The Muscle Fibers:* Not so abolished.

(Physostigmin, Veratrin, Caffein.)

EXERCISE 48.—ACTION OF DRUGS ON THE HEART.—(INTRODUCTORY).

Study in connection with Chapters XI, XII, XV, and XXII.

I. The Heart Muscle.—The cardiac muscle differs from other muscle by the fact that it contracts rhythmically by an inherent property, *i. e.*, even in the absence of nervous impulses.[1] This property is sometimes called the "*automatic motor mechanism*" of the heart. If the heart is weakened, it may be lost so that the heart may respond to stimulation by a single contraction, just like ordinary muscle. On the other hand, the rhythmic property may be imparted to ordinary muscle, for instance, by immersing it in certain solutions of NaCl. The rhythmic property therefore does not constitute a fundamental distinction between cardiac muscle and the other varieties of muscle, although under normal conditions it is a very important difference. The other properties of cardiac muscle are still more closely related to those of other muscle: its excitability, strength of contraction, tonus, etc., may be similarly affected by fatigue or by drugs; in these respects the myocardium stands intermediate between the skeletal and the smooth muscle. Normally the rhythmic contractions arise in the base of the heart — in the auricles, or in the frog in the sinus venosus; and spread gradually to the apex. Consequently the *contractions are regular,* progressing in a definite order, and all parts of the heart beat at the same rate, and the two sides of the heart contract at the same time. The explanation of these facts is, that the muscle fibers at the base of the heart are more excitable, so that they respond first to the (inherent) rhythmic stimulus; the successive areas of the ventricles contract then as the result of the stimulus started by the contraction of the auricles. If the excitability of the ventricle is increased, as the result of the action of drugs (such as digitalis, caffein, or aconite), the contraction may start in any part of the heart. *The normal rhythm is thereby destroyed,* the contractions cease to progress regularly, and the rate of each chamber of the heart may differ from the others. If the contractions arriving from the ventricles coincide with those transmitted from the auricle, the contractions are strong; if they interfere, the contractions may be weak or absent. In this way *groups* of strong contractions may alternate with periods of weak contractions. A *decrease of excitability* finds its first expression in the more sluggish ventricles. As a consequence, a summation of two or more auricular contractions may be necessary to induce a contraction of the ventricle, and the rate of the latter may be a fraction of the auricular rate. This is seen with cardiac depressants, especially in the frog's heart.

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[1] In the heart of Limulus (King crab) and perhaps in some other invertebrates, the rhythmic impulses are generated and conducted by nerves. (Carlson, 1904).

Another form of irregularity, observed particularly in frogs as the result of digitalis or aconite, consists in *peristaltic contractions,* in which the slowly traveling contraction wave is sharply marked off. This may be due to a quicker contraction, with delayed relaxation.

If the cardiac muscle of mammals is over-stimulated, the contractions become very irregular. The individual groups of muscle fibers contract independently (hence "*fibrillary contractions,*"), whilst the heart as a whole does not perform any efficient contractions. This condition, also called "*delirium cordis,*" appears to be an overquickening; it takes the place of the tetanus of the striped muscle, the mammalian heart being ordinarily unable to enter into tetanus on account of its rhythmic property.[8] The ventricles enter into delirium more readily than the auricles, because the latter are capable of a more rapid rhythmic beat, so that over-stimulation is not reached so easily. The frog's heart also does not readily go into delirium, because it is too sluggish for over-stimulation; but when its excitability is raised — as by heat — delirium can be produced.

Since the delirious heart does not keep up an efficient circulation, the mammalian heart (which is nourished by the coronary circulation) is starved and succumbs rapidly to fatigue: Delirium ordinarily produces paralysis of the heart, unless the coronary circulation is sustained artificially. The rabbit's heart may recover spontaneously; the dog's heart does not.

The state of the *coronary circulation* is very important for the mammalian heart, as its great activity demands a liberal nutrition. The effect is mainly upon the strength of the contractions, the rate being but little altered. Consequently all agencies which depress the heart directly, also depress it indirectly by lessening its food supply; and vice versa. An increased tonus of the heart by lessening the excursions also starves the heart, so that a strong stimulation of the cardiac muscle may rapidly paralyze it, by interfering with the coronary circulation; and systolic standstill is consequently impossible in the intact mammalian heart, since the starved muscle cannot sustain the systole.[1] A strong contraction of the myocardium also causes a mechanical compression of the coronary vessels, thereby lessening the bloodflow through them. On the other hand, extreme dilation of the heart also lessens the coronary circulation; so that an overdistended heart may often be improved by withdrawing some blood. Since the coronary vessels possess vasoconstrictor and vasodilator nerves, they may be affected by drugs acting centrally or peripherally on the vasomotor mechanism.[2] The coronary circulation may also be modified *indirectly* through changes in the general arterial pressure. Vasoconstrictors will therefore stimulate the heart,[3] and vasodilators will depress it. In the excised heart these agents may have the opposite effects, since they act then on the coronary arteries alone; but in the intact animal the effects on the circulation at large will overcome the effect on the muscle of the coronary arteries.

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[8] **Tetanus of the mammalian heart can be produced only by the simultaneous stimulation of the vagus and cardiac muscle.**

Changes in blood pressure have also a mechanical effect on the heart: The cardiac muscle, like other muscles, contracts better against a certain resistance than against no resistance. This resistance is furnished by the aortic pressure. The normal blood pressure seems to furnish the optimum resistance to the normal heart, so that it would be a mistake to consider that a fall of pressure, by lessening its work, would increase the force of a *normal* heart. With a *weakened* heart, however, the optimum resistance falls, so that a diminished pressure is really beneficial to an exhausted heart.

The *amplitude of the contractions* is controlled, not only by the force of the heart, but also by its tonus, by its rate, and by the blood pressure. A tonus which is greatly increased or diminished will prevent the muscle from relaxing or from contracting to the usual extent. An increased rate does not allow time for complete contraction and relaxation, and so renders the beats more shallow, whilst a slow rate tends to increase the excursions. A high blood pressure prevents the complete emptying of the heart, and thereby renders the beats more shallow and slows the rate. (In intact animals this slowing is very marked, being due to a reflex stimulation of the vagus mechanism.)

The *volume of blood thrown out at each beat* varies with the amplitude of the excursions. The *output in a given time* is the product of the rate, and the volume of each beat. The *work done by the heart* is the product of the output, and the resistance (blood pressure) against which it acts.

Effect of the Rate of the Heart on the Output.— The output of the heart is greatly diminished by slowing its ordinary rate; the increased volume of each beat being insufficient to counterbalance the lessened number of contractions. A quickening of the heart, on the other hand, causes but little increase in the output, since the lessening of the volume of each beat nearly offsets the increased rate. This, as well as the effect of the vascular system, etc., may be demonstrated on an artificial circulation apparatus (consult Exercise 53).

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[1] The mannualian heart is, however, capable of systolic standstill, if the coronary circulation is maintained by artificial means, as in Langendorff's method (see exercise 78).

[2] In working with artificially prepared heart, it is important to remember that the coronary vessels are also affected by *the temperature of the blood;* being dilated by heat and constricted by cold. The temperature has an even greater effect on the cardiac muscle itself, heat quickening the rate, whilst cold slows the contractions.

[3] Rhythmical beats may be produced in the excised mammalian heart by simply raising the intracoronary pressure by indifferent gases (hydrogen, Magnus, 1902) or oil (Sollmann, 1906).

II. The Innervation of the Heart.—Although the cardiac muscle is able to perform regular rhythmic contractions in the absence of nerves, it is normally under nervous control. Besides the sensory (depressor) nerve these are two motor nerves, the vagus, and the accelerator branch of the sympathetic. The origin (center) of both of these nerves is in the medulla. Both nerves run in the same sheath in the frog (Fig. 99, page 800), but are separated in mammals. Both nerves are connected with ganglia. Those of the vagus are contained in the heart itself (in the frog these vagus ganglia are situated especially at the juncture of the sinus venosus with the auricle). Those of the accelerator are extra-cardiac, and in mammals lie probably in the inferior cervial and in the stellate ganglia, around the subclavian artery. The endings in the cardiac muscle are " free endings," similar to those of unstriped muscle. The heart contains no structures corresponding to the end plates of striped muscle.

The effect of electric *stimulation* of these nerves appears only after a slight latent period, and disappears after a time, even if the stimulation is continued. The latent period and the action are longer for the vagus.

Moderate vagus stimulation causes a slowing of the rate, the diastole being especially prolonged. The irritability and the contractile power are increased in mammals; the amplitude of the excursions is larger; the tonus is diminished; the blood pressure and output fall. *Strong stimulation* causes diastolic standstill.

Accelerator stimulation (the anterior ramus of the annulus of Vieussens) quickens the rate, shortening all the phases except the auricular systole and the ventricular diastole. The excitability, tonus, and strength of the heart are increased, but the beats are more shallow in mammals (in the frog the excursions are also increased). The blood pressure and the output rise somewhat, but not commensurate with the increased rate.

Tonic Impulses.—The vagi are tonically active in some animals (notably in man and in dogs), so that division of these nerves causes a quickening of the heart. In other animals (rabbits) there is normally no tonic action, so that division produces little effect on the heart rate. The accelerators are also tonically active, but division of these nerves produces less effect than section of the vagi. The ganglia and endings also have some tonic action, for a further quickening may be obtained, after section of the vagi, by paralyzing the vagal endings.

The vagi or accelerators may be stimulated or depressed directly, at their origin, or in any part of their course, by drugs or by other means. They can also be affected *indirectly*, especially the vagus. A fall in blood pressure, most forms of reflex irritation, muscular exercise, swallowing, etc., quicken the heart by inhibiting the vagus center. Stimulation of the trigeminal endings, on the other hand, excites the vagus center and slows, or even stops, the heart. A rise of blood pressure also stimulates the vagus and causes slowing.

III. Methods of Studying the Actions of the Heart.—It follows from the preceding that the action of the heart depends on a considerable number of interrelated factors. These, acting together, produce the phenomena which may be studied on normal animals by the pulse and apex-beat; and on operated animals by direct observation and tracings of the exposed heart. The intracardiac and the general blood pressure and the output of the heart, etc., are also determined in large part by the cardiac activity; but since they also depend on the state of the vasomotor system, they must be supplemented by more direct methods. Indeed, all the observations on intact animals give only the sum of the factors which may be involved. It is evident that no understanding of the action of a drug is possible until the share of each factor is known. This must be determined by isolating it as completely as possible from the other factors.

Suitability of Different Animals.— The hearts of frogs and turtles are convenient for studying the effects of drugs, since they continue beating normally for a considerable time after they are exposed or excised. Many phenomena can be observed very well by direct inspection, others may be recorded by levers, etc. The *Williams Apparatus* (Fig. 123) has been used a great deal in pharmacologic work on the frog's heart, as it permits the study of a number of phenomena under a variety of conditions. An artificial circulation is maintained through the ventricle, by means of solutions, to which the poisons may be added. The apparatus consists of a reservoir and a system of tubes provided with slit valves (*V* and *V'*) and a two-way cannula. These allow the perfusing liquid to get into the heart (*H*) and to be pumped in a definite direction. The cannula is introduced through the bulbus aortæ into the ventricle and tied. (The apex of the ventricle may be used alone.) Each contraction of the ventricle forces the blood through *V'* into the upright tube, and from here into the reservoir. The relaxation of the heart allows the liquid to enter from *V*. The auriculoventricular valves prevent the blood from coming back into the auricle. The number of drops flowing into the reservoir can be counted, and give an idea of the work done. By raising or lowering the reservoir the intracardiac pressure can be varied;[2] by applying the screw-clamp beyond *V'* one may introduce resistance; by clamping this tube altogether and opening communication to a small mercury manometer the absolute pressure can be measured and tracings taken. The changes in volume, corresponding to the extent of the excursions, may be read from the millimeter scale, *MS*. (Williams, Jacobj, Wood and Hoyt).

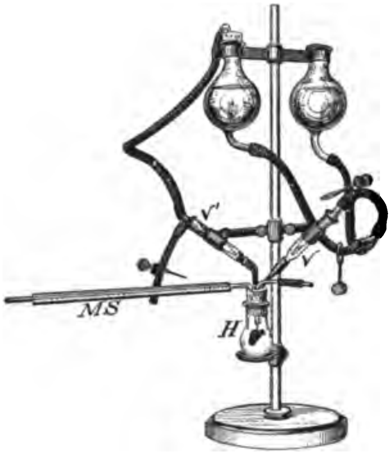

Fig. 123.— Williams' heart apparatus.[1]

The *cardiac nerves* of frogs are also situated conveniently. It must not be forgotten, however, that the *physiology of the heart of cold-blooded animals differs considerably from that of the warm-blooded;* and caution must be used in applying the results obtained with the one to the other. The main uses of the frog's heart are therefore restricted to preliminary studies, to the investigation of special problems, and to the convenient demonstration of actions which have been already controlled on warm-blooded animals. Amongst the latter, the functions of the myocardium are identical, as far as we know. The absence of tonic vagus impulses in rabbits must be borne in mind.

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[1] The valve *V'* should point in the reverse direction. Fresh frog's skin is convenient for these valves.

[2] A pressure of 200 mm. of water is the optimum.

Drugs may act on the heart in three ways: (1) Directly on the cardiac muscle; (2) directly on the cardiac nerves; and (3) indirectly, on either the muscles or nerves — through reflexes, altered resistance, altered nutrition, altered coronary circulation, etc.

Methods of Studying the Direct Effects on the Cardiac Muscle.— These demand that the resistance to the work of the heart be kept constant — an object which can only be accomplished by separating the heart from the general vascular system. The pulmonary circulation may generally be kept intact, as it is not much affected by drugs. The methods of isolating the heart may, however, be conveniently divided into those which retain the pulmonary circulation, and those which do not. The nervous mechanism should also be excluded. If it is desired to retain the intracardiac nervous apparatus, it suffices to cut the trunks of the vagi and accelerators, or to shut off the blood from the medulla. The intracardiac vagus mechanism can also be paralyzed by atropin. This leaves only the accelerator endings (see page 893).

The frog's heart will continue to beat for some time after it has been excised from the body; but the mammalian heart requires that the coronary circulation be maintained. This may be done by the heart itself, or by injecting the perfusion fluid under pressure.

IV. The Isolated Mammalian Heart.— The methods which have been employed for the study of the isolated mammalian heart are briefly as follows:

I. Methods employing the whole heart and pulmonary circulation (excluding the peripheral vessels and, to a large extent, the brain) (Fig. 124). These methods differ by the manner in which the action of the heart is observed or recorded, which may be done by direct observation, by taking pressure curves from the carotid or from the ventricles, or by the myocardiogram. The methods consist essentially in establishing a connection between the large arteries and large veins, and then ligating the vessels peripherally to this connection. The vessels which are employed for this purpose and the apparatus used for establishing the connections vary in the different methods:

(*a*) *Communication established between the aorta and right auricle:*

1. *Martin's Original Method.*— In this, a communication is established through a reservoir containing defibrinated blood and connected with the right auricle, while the left ventricle pumps the blood through a tube back into the reservoir. The course of this blood then is: right auricle, pulmonary circulation, left heart, standing tube, and reservoir. The oxygenation of the blood is effected by artificial respiration.

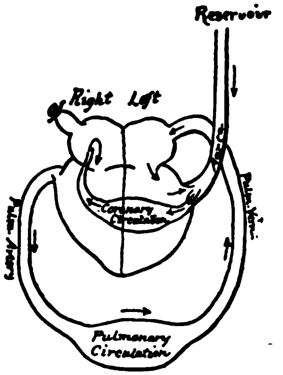
2. *The modified method of Martin and Applegarth* establishes a communication through the coronary vessels, the maintenance of pressure being aided by connection of the aorta with a reservoir containing defibrinated blood. The course of the blood is: aorta, coronary circulation, right heart, lungs, left heart, and aorta. Oxygenation is by artificial respiration.

3. *The McGrath and Kennedy method* is an amplification of the last, in that it measures the intracardiac pressure and the outflow through the pulmonary artery.

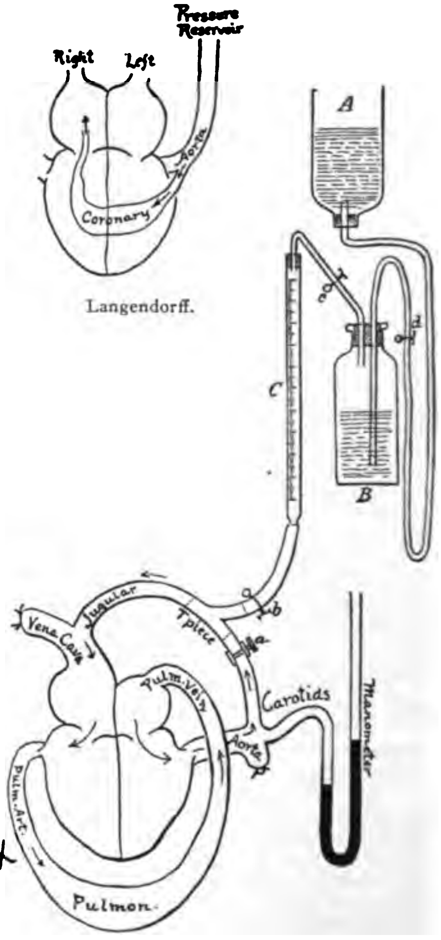
4. *Hedon and Arrous' method* differs from the preceding methods by leaving out the reservoir, simply tying the aorta and its branches and the vena cava. The course of the blood is: aorta, coronary circulation, right heart, pulmonary circulation, left heart, and aorta. Oxygenation is by artificial respiration.

The heart survives some hours. It becomes progressively slower by the using up of material and the production of waste products, but it remains regular.

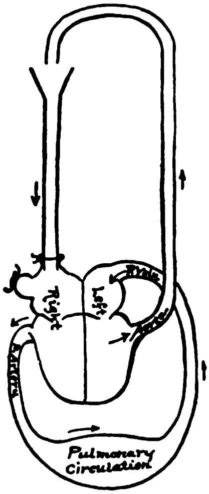
5. *Cyon* connects the aorta with the vena cava. In addition, he is very careful to ligate all the vessels leading to the brain, so that he can expose this organ to poisons without their reaching the general circulation.



Martin and Applegarth. *Tschitowitch* connects the pulmonary artery and vein by a tube.



Langendorff.



Martin's original method.

Bock.

Fig. 124 — Methods of studying the isolated mammalian heart.

(*b*) *Communication Through the Carotid and Jugular.*— The methods differ mainly in the mechanism introduced as resistance, this being either constant or variable:

1. *Stolnikow* makes the connection through two glass vessels of known content, which are reversible, and one of which is alternately filled by blood expelled from the heart, while the other empties into the vena cava. In this way the volume of blood expelled by the heart in a given time can be measured. The other vessels are, of course, ligated. Oxygenation is by artificial respiration.

2. *Bohr and Henriquez* establish the connection by a simple tube. *Hering* does not ligate the veins, using them as a pressure regulator. *Bock* forms the connection through a compressible tube and screw cock, so that a varying resistance may be introduced.

In all these methods the registration is done by a manometer in the other carotid, the aorta and vena cava being ligated and artificial respiration being kept up.

III. Completely isolated hearts; *i. e.,* without the pulmonary circulation, but with the ganglia still active. In these methods the blood must be artificially oxygenated, and is usually introduced under pressure. Otherwise the methods are similar to the preceding.

1. *Tschitowitch* uses practically Martin's original method, connecting the pulmonary artery with the pulmonary vein by a tube, the course of the blood being: reservoir, jugular vein, right heart, connecting piece, left heart, aorta, and reservoir.

2. *Langendorff* uses only the coronary circulation, introducing the blood into the aorta under pressure, from which it goes through the coronary circulation and flows out of the right heart. The shape of the heart, number and strength of beats, and the number of drops flowing through the right heart may be measured in this way.

3. *Hedon and Arrous* ligate the aorta and vena cava and connect the pulmonary artery and pulmonary vein directly, feeding the heart with its own blood and keeping it alive by artificial methods.

4. *Heymans and Kochmann* connect the aorta of the excised heart with the carotid of a second animal, letting the blood return through a funnel connected with the jugular; or without the use of a funnel, by connecting the pulmonary artery of the excised heart with the jugular of the animal, and tying the other vessels.

IV. Isolated apex preparations; *i. e.,* ganglion-free heart muscle. *Porter* has succeeded in maintaining rhythmic contractions of isolated strips of the apex of the heart by injecting oxygenated blood under pressure into a branch of the coronary artery supplying it.

The methods of Langendorff and Porter have been criticized as yielding abnormal results, because they leave the cavities of the heart empty. Their results must therefore be interpreted cautiously. *Gottlieb and Magnus* (1903) obviate this difficulty by filling the ventricle with a distensible baloon.

Perfusion Liquids.—In perfusing the excised heart, a fluid must be employed which does not produce any salt or ion action, which contains oxygen and nutriment, and which is at body temperature. The best is oxygenated defibrinated blood from the same species of animal, diluted with 5 volumes of normal saline solution. Other fluids may be substituted, but these must be charged with oxygen, when used with the mammalian heart. Serum may be employed. An excellent substitute is *Locke's Fluid* (see Index). By the use of Langendorff's or Porter's method, the heart can be kept beating, or revived, many hours after death.

Similar solutions may be used for the perfusion of frogs' hearts, except that they should contain less salt (0.6 to 0.75% NaCl). Used alone, this saline solution gradually poisons the heart after the manner of digitalis. The toxicity is less if 2% of gum arabic is added, or small quantities of some other salts. *Ringer's solution* (see Index) has been found very good. Rabbit's or beef's blood, defibrinated and diluted with 2½ parts of 0.6% NaCl, is also used.

V. Analysis of the Effects on the Heart.—Actions on the Nervous Mechanism can be studied with the heart in situ, by dividing or stimulating the vagi and accelerators at different levels. Cyon has also devised a method of studying the effects of drugs upon the cerebral cardiac centers by separating these from the general circulation and artificially circulating through them defibrinated blood containing the poisons to be studied; in this way they do not reach the heart at all.

An effect upon the nerves is manifested particularly by changes in the rate of the heart; but as the rate may also be modified through the muscle, or indirectly, a more detailed analysis becomes necessary; this will repay closer study, as it illustrates the methods of pharmacologic research.

Investigation of Changes in the Rate of the Heart.— (A) Quickening may be due to a direct or reflex inhibition of the vagus, or to stimulation of the accelerator nerves, or of the cardiac muscle.

(1) If the quickening does not occur after section of the vagi, it must have been due to *central paralysis of the vagi.* If the center does not respond to reflex stimulation (such as the inhalation of ammonia with rabbits), the center itself is paralyzed. If it does respond, the inhibition of the vagus must be *reflex,* which can be further demonstrated by division of the corresponding path.

(2) If the quickening occurs after section of the vagi, the drug is tried on animals in which the vagus endings have been completely paralyzed by atropin. If it produces no effect, the drug must paralyze either the ganglia or endings. It is tried on animals in which the ganglia have been paralyzed by nicotin; or on the ganglion-free apex of the frog's heart. If it produces no quickening, it must have *paralyzed the vagus ganglia;* if quickening occurs, it must *paralyze the endings.* In the former case, stimulation of the sinus, in the frog, stops the heart; if the endings are paralyzed stimulation of the sinus has no effect.

(3) If the quickening occurs even after atropin, there must be a stimulation of either the accelerator mechanism or of the cardiac muscle. If the effect occurs on the *excised* atropinized heart, it must stimulate either the *muscle or the accelerator endings.* It is very difficult to distinguish between these: the study of the relative duration and strength of the phases of the cardiac cycle furnishes some indication. The cardiac muscle, quite free from nerve endings, can also be studied in the embryonal chick. It appears, from these methods, that the stimulation is always of the muscle, rather than of the endings, so that we shall designate a quickening obtained after atropin as a *stimulation of the cardiac muscle.*

(4) If the drug acts after atropin, but has no effect on the excised heart, it must *stimulate the accelerator center.* This can be further shown by its producing no effect on the intact animal if the spinal cord is divided above the first dorsal vertebra, or if both stellate ganglia are excised.

(B) Slowing may be due to direct or reflex stimulation of the vagi; to paralysis of the accelerators; to paralysis of the muscle, direct or through impaired nutrition; or to systolic stimulation of the muscle.

1. If the slowing does not occur after section of the vagi, it must be due to a *stimulation of the vagus center,* especially if electric stimulation of the vagus trunk continues effective.

2. If it occurs after section of the vagi, but not after nicotin, it must be due to *stimulation of the vagus ganglia.*

3. If it occurs after section of the vagi and after nicotin, but not after atropin, it must be due to *stimulation of the vagus endings.* Electric stimulation of the vagus trunk is ineffective in 2 and 3.

4. If it occurs after atropin, but not after division of the accelerators, it must be due to a *depression of the accelerator.* If electric stimulation of the accelerator nerve is effective, the depression must be *central;* if not, it is *peripheral.*

5. If it occurs after atropin and after division of the accelerators, it must be due to a direct action on the cardiac muscle, or to *insufficient nutrition.* The latter may be excluded by artificial circulation. If the slowing persists, it is due to *paralysis,* or to *increased tonus,* of the cardiac muscle; the strength of the contractions will indicate which is the true explanation.

(C) Cardiac Standstill may be due to stimulation of the vagus, to paralysis of the cardiac muscle (and in frogs, to excessive systole).

1. If the standstill disappears on section of the vagi, it is due to *stimulation of the vagus center.*

2. If it persists, but disappears after atropin, it is due to *peripheral stimulation of the vagus.* The ganglia and endings can be distinguished as in (*B*) (2 and 3). The frog's heart is strongly diastolic if the stoppage is due to stimulation of any part of the vagi.

3. If atropin does not relieve the standstill, it is caused by a *direct effect on the muscle.* In mammals, this is always paralytic. In frogs it may be due to *paralysis,* when the heart is of medium size, and cannot contract if it is forcibly distended; or to *excessive systole* (Digitalis group) when the heart is very small, and contracts if distended.

4. The paralysis may only involve the *rhythmic power,* so that the heart responds to stimulation (*i. e.,* a pin-prick) by a single contraction; **or it may** be complete.

EXERCISE 49.— EFFECTS OF DRUGS ON CARDIAC MUSCLE, FROG AND TURTLE.

Study in connection with Chapters XV, XVI, XIX, XXII.

Read technic, pages 799 to 801.

Also consult Exercises 74 to 76.

Materials Needed (for entire class).— 20 frogs; 12 turtles; 3 induction coils; 2 perfusion apparatus and cannulæ; 12 frog boards; 12 light muscle or heart levers (4 arranged to rest on the heart); 12 frog needles; ligatures; 12 pipettes; 12 drums; pins; 3 watch-glasses. 0.75% saline solution; Tr. Digitalis, Tr. Aconite, Adrenalin (5 c. c.); KCl, 9% Alcohol (25 c. c.); 1% Caffein (25 c. c.); Ringer's Fluid (1 L.). The following dissolved in 0.75 saline (5 c. c. of each): Digitalis, 4 and 20% infusion; Aconite, 4% infusion; $BaCl_2$, 1%; Strychnin, $^1/_{100}$%; Chloroform and Ether (saturated); Quinin, 1% and $^1/_{10}$%.

Experiments.— There may be distributed amongst the sets as follows (five sets suffice to demonstrate the principal drugs and methods):

Set A = A 1 and Ca 3; Set B = B 2 and Cb 4; Set C = A 6 and F 1; Set D = D; Set E = E; Set F = A 2 and F 2; Set G = B 1 and Cb 3; Set H = A 3 and Cb 1; Set I = B 3 and Ca 2; Set K = A 4 and Cb. 2; Set L = B 4 and Ca 1; Set M = A I (Barium) and Ca 4.

A. Inspection of Exposed Heart, Local Application.— *General Directions.*— Pith the brain of a frog (page 795) and pin on board. Expose the heart (page 799) and trim away the pericardium. Count the rate and observe the size, the relative strength of systole and diastole, the color and regularity. Irrigate the heart with the solution, from a pipette, and repeat the observations and the application of the drug every five minutes during an hour, or as long as the heart survives. Record the results in the form of a curve, as in Fig. 125, the abscissæ corresponding to the rate, the ordinates to the time.

1. **Digitalis.**— Apply 4% infusion (Figs. 125 and 88, page 484). The effect consists in an increased tone of the cardiac muscle; the beats are slowed (sometimes there is a preliminary quickening) and strengthened. The systole particularly increases, the heart becoming progressively smaller and whiter. The contractions then become irregular, and often peristaltic. The slowing continues and affects particularly the ventricle, so that there may be several auricular beats in each contraction of the ventricle. Finally the heart stops in systole, *i. e.,* as a small white lump. It may be necessary to apply a 20% infusion to obtain this result. If the ventricle be distended by injecting 0.75 saline under pressure (with a hypodermic syringe), it will again contract. The application of aqueous camphor solution, or pricking with a needle, starts only a few beats. Veratrin (½%) or $BaCl_2$ (1%) give effects very similar to digitalis.

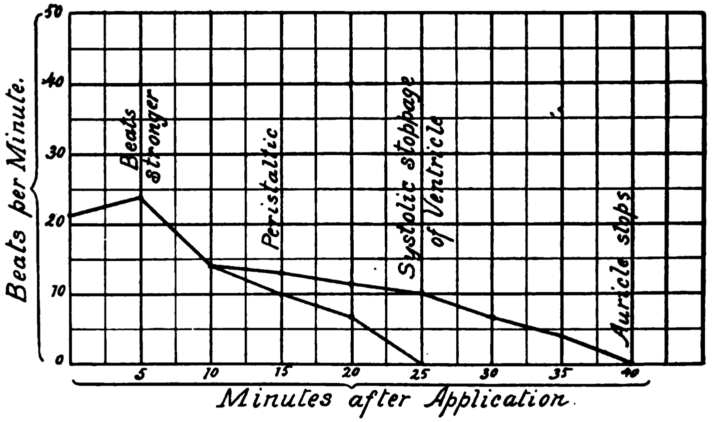


Fig. 125.— Diagram of observations on the effect of digitalis, frog's heart.

The results are sometimes atypical.

2. **Aconite.**— Apply 4% infusion. This stimulates and then paralyzes successively the accelerators, vagus, and muscle (see Fig. 67, page 320). If the results are typical the rate is first quickened, then slowed, then again quickened and irregular, and then gradually slowed with final paralysis in the median position. The primary quickening may be absent. The secondary quickening is fairly constant and characteristic. The most striking feature is the extreme irregularity and arhythmia of the heart in the later stages. This may take the most varying forms. The two sides of the ventricle often beat alternately, the blood being pumped from one side to the other.

3. **Strychnin.**— Use $^1/_{100}$%. This has practically no effect, demonstrating that this alkaloid is not a cardiac stimulant in the strict sense.

4. **Quinin.**— Use $^1/_{10}$%. The heart is slowed and finally stops in

median position, by paralysis of the cardiac muscle. The action is analogous to that on skeletal muscle (consult Exercise 45).

5. Anesthetics.— Excise the hearts of six frogs. Place two hearts into each of three watch-glasses containing the following normal solutions: (*a*) Normal saline; (*b*) normal saline saturated with chloroform; (*c*) normal saline saturated with ether. Note that the chloroform stops very quickly, the ether heart much later. The stoppage is in the median (paralytic condition), and is preceded by slowing and weakening. If the hearts are at once removed to normal saline, they may beat again.

The greater toxicity of the chloroform is emphasized by the fact that it is much less soluble than ether, the saturated solution containing only a twentieth as much of chloroform as of ether.

B. Systemic Administration.— The drugs may be injected into the dorsal lymph-sac, just before pithing and exposing the heart. The results are practically identical with those of direct application. The following may be used:

1. *Tr. Digitalis*, 1 c. c.
2. *Tr. Aconite*, 1 c. c.
3. *Strychnin*, 1 c. c. of $^1/_{100}$%.
4. *Quinin*, 1 c. c. of 1%.

C. Tracings (*Turtle's Heart*)—(*a*) Suspension method.— Arrange the heart for tracings by the suspension method (see page 800) and apply the drugs as in A, 1, 2, 3, and 4.

(*b*) Rest the lever on the heart (see page 800) and apply the drugs as in A, 1, 2, 3, and 4.

D. Perfusion of Frog's Heart.— Arrange the heart for perfusion (see page 800). Observe the results or take tracings by the suspension method (see page 800). Use *Digitalis*, 1% of the 4% infusion. (KCl and adrenalin (see No. E) or alcohol (5%) may be substituted.)

The Williams heart apparatus (Fig. 123, page 894) can be demonstrated.

E. Perfusion of Turtle's Heart.— See technic, page 801.

Employ *KCl*, 0.9%; the heart is arrested.

Substitute adrenalin, 1 : 50,000; the heart revives. (Add 1 : 50 of 1 : 1,000.)

(Digitalis or alcohol may be used instead, see No. D.)

F. Strips of Turtle's Ventricle.— See technic, page 801.

Use 1. Alcohol, 2, 5, and 10%.
  2. Caffein, 0.01 and 0.1% (see Fig. 50 *C*, page 165).

(Strychnin, 0.01%, or Digitalis, 0.001%, may be substituted.)

Summarize the effects of Quinin in Chapter XXXVIII, No. 13.

EXERCISE 50.— CARDIAC NERVES IN THE FROG AND TURTLE.

Study in connection with Chapters XI and XII.

Read the technic, page 800.

Experiments.— Half the sets may do I, the others II.— **1. Stimulation and Paralysis of Vagus Endings.**— (*a*) Pith the brain of a frog, pin on board, expose heart and remove pericardium. Note that electric stimulation of the sinus venosus stops the heart (stimulation of vagus ganglia).

(*b*) Apply atropin: In a few minutes, stimulation of the sinus produces no effect (paralysis of vagus endings). The atropin may cause a quickening of the heart by stimulating the muscle.

(*c*) Wash off the atropin with normal saline. Apply muscarin (or physostigmin); sinus stimulation is again effectual, and heart may be slowed (stimulation of vagus endings and cardiac muscle).

(*d*) Wash with normal saline and repeat (*b*); same effect. Atropin and muscarin (or physostigmin) have antagonistic actions, and whichever is used in larger quantities can overcome the effects of the other. This holds for all peripheral structures upon which these alkaloids act.

II. Stimulation and Paralysis of Vagus Ganglia.— (*a*) Pith the brain of a turtle, pin on board, and expose the heart and remove pericardium. Expose the vagus trunk (see page 800). Note that electric stimulation of the vagus trunk slows or stops the heart.

(*b*) Apply nicotin, or pilocarpin. The heart is first slowed (stimulation of vagus ganglia), then quickened (paralysis of these ganglia). Stimulate the vagus trunk; no effect. Stimulate the sinus; the heart is slowed or stopped. (This shows the location of the paralysis. Explain.)

Summarize the action of Muscarin, Chapter XXXVIII, No. 25.

Material Needed (for six students).— Frog; turtle; pins; dissecting tools; 2 pipettes; 2 induction coils connected for tetanizing current. 2 c. c. of each of the following alkaloids: $^1/_{10}$% solution of the salt in 0.75% NaCl: Atropin, Muscarin or Physostigmin, Nicotin, Pilocarpin; 25 c. c. 0.75% NaCl.

EXERCISE 51.— EFFECTS OF DRUGS ON BLOOD VESSELS.

Study in connection with Chapters XIII, and XXI to XXIII.

Consult also Exercises 71 to 73.

Explanatory.— This subject will be studied in detail in the next chapter, since it generally requires operative procedures. Some of the effects may be observed, however, in intact animals, by inspection, and in frogs.

Experiments.— The experiments may be demonstrated, or distributed amongst the sets. (Consult Exercise 27, No. 3.)

1. Ergot on Comb of Rooster.— Administer to a rooster 5 Gms. of powdered ergot (rolled into a cartridge with tissue paper) by mouth, or 5 c. c. of fluidextract hypodermically. Within an hour the tips of the combs and wattles will become cool and blacken. This may persist for several days and may pass into dry gangrene of the affected parts. The result is due to a persistent vasoconstriction, resulting from a direct action on the arterial muscle. (The experiment is often unsuccessful, if the ergot has become inactive, or if the animal is not very susceptible.)

2. Vasodilation from Depression of Vasoconstrictor Ganglia.— *Vasoconstriction Through Reflex Stimulation* (Nicotin).— Inject two white rabbits, each with 10 mg. per Kg. of nicotin (1 c. c. of 1% per Kg.). In about ten minutes the ear vessels are seen to dilate. (Depression of the sympathetic ganglia.) Apply reflex stimulation (blowing on the rabbit): the vessels constrict at once; after a short time they dilate again, and the experiment may be repeated indefinitely. (The small dose of nicotin used in this experiment produces a de-

Materials Required (for entire class).— 3 frogs; 2 microscopes; frogboards; pins; 2 tumblers; pipettes; dissecting tools; plethysmographs; oncographs; hypodermic syringe; rooster with large comb; 2 white rabbits; dog; frog's perfusion apparatus. ½% Curare (10 c. c.); Tr. Digitalis (25 c. c.); 1% Nicotin (10 c. c.); Ergot (or fluidextract), (5 Gm.); Ringer's Fluid (400 c. c.); 10% Sodium Nitrite (25 c. c.).

pression of the ganglia sufficient to block the weak tonic vasoconstrictor impulses which pass normally to the muscle; but it is not sufficient to block stronger impulses, as those due to reflex stimulation. Larger doses of nicotin block these impulses also.)

The *general effect* of nicotin may also be observed on this animal (compare Exercise 24, No. 3 *a*). The reflex excitability is first increased, then the animal shows a condition of partial paralysis, with convulsions on stimulation. There may be nausea. The pupils are variable.

3. Digitalis on Vessels of Frog's Foot.— Curarize a frog (see Exercise 42, No. 1). Pin on board to observe circulation in foot (Oc. III, obj. III). Make an exact drawing of a small vessel. Inject into lymph-sac 0.5 c. c. of tincture (10%) digitalis and observe the same vessel from time to time and note changes in its diameter. A marked vasoconstriction (about 25%) is usually observed.

More exact results can be obtained by using a camera lucida or an eye-piece micrometer.

4 Adrenalin on Mesenterin Vessels, Frog.— See technic, page 796. Apply $^1/_{100}$% adrenalin and observe the constriction. (This experiment may be modified to show the action of astringents, by first inducing an inflammation and then applying 1% alum.)

5. Artificial Perfusion, Frog.— Pith a frog, brain and cord, and perfuse the vessels of a frog (see page 801) with Ringer's Fluid. Observe the rate of flow. Substitute 1 : 2,000 sodium nitrite: The flow is quickened. Substitute 1 : 100 of Tr. Digitalis: The flow is slowed. Do these drugs act centrally or peripherally? (Any of the solutions mentioned in Exercise 73 may be employed.)

EXERCISE 52.— EFFECTS OF DRUGS ON THE PULSE.

Explanatory.— The circulatory effects of drugs can be studied to some extent by observing the rate, strength, regularity, etc., of the pulse; the observations can be made more exact by employing a sphygmograph, cardiograph, sphygmomanometer, and plethysmograph. These experiments should be made on man. They are left to volunteers, but the student will find them most instructive if he performs as many as possible on himself. The doses are chosen so as to produce but a moderate therapeutic effect, devoid of all danger (except perhaps in severe circulatory disease). It would also be very useful to repeat the observations on well-selected ward cases.

Observations Required.— Rate, character, tension, rhythm, and regularity of the pulse. Rate of respiration. Incidental effects (headache, bowels, etc.). Other effects as noted in the experiments. The drugs should be taken an hour after meals, the subject remaining perfectly quiet during the period of observation; this should extend over several hours. Several observations of the normal conditions should be made before the drug is taken.

Experiments (Optional).— 1. Let a rabbit inhale *ammonia;* note that the heart stops by reflex stimulation of the vagus center, through irritation of the trigeminal (consult Exercise 28, No. 1). This effect is sometimes produced by the inhalation of chloroform and constitutes one of the causes of death during anesthesia (Fig. 81, p. 429).

2. Take 0.3 c. c. of tincture of *digitalis:* In about half an hour the

Material Needed.— Sphygmograph, Plethysmograph, Sphygmomanometer, Rabbit. *Drugs* (best in the form of tablets): Digitalis (0.3 c. c. of tincture); Atropin (1 mg.); Aconite (0.3 c. c. of 10% tincture); Amyl Nitrite (3 drop pearls).

pulse will be somewhat slowed, with increased tension. Stimulation of vagus and of cardiac and arterial muscle.

3. Take 1 mg. of *atropin:* quickening of pulse (depression of vagus endings), rarely preceded by slowing. Dilatation of pupils, dryness of mouth, absence of perspiration (depression of the corresponding endings). Sometimes a little headache. The effects begin in about 20 minutes, and reach their maximum in about an hour, and last some six or eight hours.

4. Chew a tablet containing 0.15 c. c. of tincture of *aconite.* Note the prickly sensation of the tongue. In about half an hour the pulse is somewhat slowed, and the tension lowered. (Stimulation of the vagus center.)

5. Crush the *Amyl Nitrite* pearl in a handkerchief (or drop on 3 drops) and inhale. At once the face flushes (note the extent of the reddened area); the head throbs; the heart is quickened; the tension is lowered, the dicrotic wave is more prominent (Fig. 84, page 472). (Vasodilation, inhibition of vagus tone.)

EXERCISE 53.—ARTIFICIAL CIRCULATION SCHEMA.

Study in connection with Chapter XXII.

Explanatory.— The effect of changes in the heart and blood vessels on the blood pressure and blood-flow can be demonstrated in a most instructive manner by the circulation model depicted in Fig. 126.

Experiments.— Make the following observations and record them in tabular form. The time can be kept with a metronome. The pumping should be continued for a short time before observations are taken. Students A and B, reading of arterial and venous pressure; students C and D, pumping and outflow; students E and F, recording.

	Arterial Pressure.		Venous Pressure.		Outflow (at v.). (Time required for 100 c.c.)
	Max.	Min.	Max.	Min.	
1. (*Normal*) Pump with moderate excursions; at rate of 60 per minute. The capillaries-clamp is partly closed.............					
2. (*Vagus Stimulation*) Pump at the rate of 10 per minute, allowing complete relaxation, but incomplete contraction...	Falls.		Falls.		Falls.
3. (*Vagus Depression*) Pump at the rate of 120 per minute, but with very weak compression	Little rise.		Little rise.		Little rise.
4. (*Digitalis action on Cardiac Muscle*) Pump at the rate of 30 per minute, causing complete contraction, but incomplete relaxation.............	Rises.		Rises.		Rises.
5. *Simultaneous stimulation of Vagus and Cardiac Muscle* (*Digitalis*).— Pump at the rate of 30, with complete contraction and relaxation......	Rises.		Rises.		Rises.

Material Required.— Artificial circulation apparatus (see Fig. 126) water colored with carmine or blood; Metronome; 100 c. c. graduate.

	ARTERIAL PRESSURE. MAX. MIN.	VENOUS PRESSURE. MAX. MIN.	OUTFLOW (AT V.). (Time required for 100 c.c)
6. *Vasoconstriction.*— Repeat 1, then tighten the capillaries-clamp	Rises.	Falls.	Falls.
7. *Vasodilatation.*— Open the capillaries-clamp	Falls.	Rises.	Rises.
8. *Complete Digitalic Action.*— Combine 5 and 6	Rises more than 5 or 6.	Rises less than 5, more than 6.	Rises less than 5, more than 6.

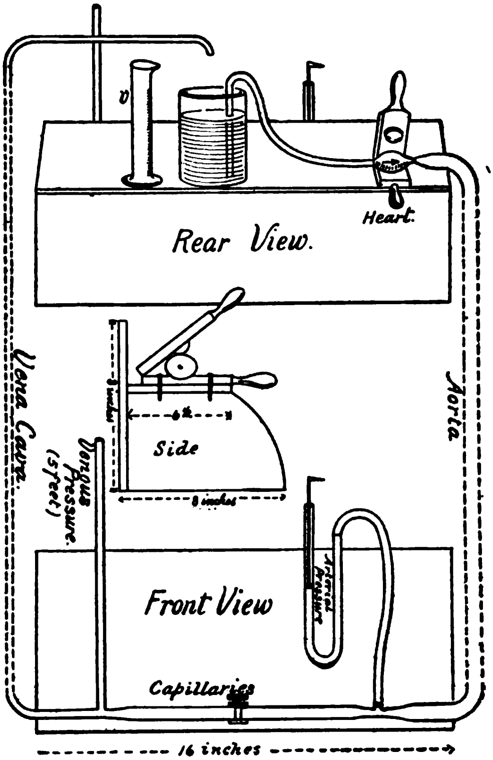


Figure 126 Artificial Circulation Model: The heart is represented by a rubber syringe bulb with valves in the direction of the arrow. This is compressed by a lemon-squeezer. The vessels are formed by rubber-tubing, that for the aorta being especially elastic. The arterial pressure is taken on a mercury manometer; the vein pressure by an upright tube filled with water. The capillary resistance is furnished by a screw clamp. The dimensions of the apparatus are indicated on the figure.

EXERCISE 54.— EFFECT OF DRUGS ON THE PUPIL.

Study in connection with Chapters XI and XII.

Explanatory.— The iris contains two sets of smooth muscle fibers, the circular sphincters and radial dilators (Fig. 56, page 231).

The sphincter muscle is innervated by fibers contained in the oculomotor nerve. These terminate around the cells of the ciliary ganglion. From here the fibers pass on as the short ciliary nerve.

The nerve fibers for the radial muscles run in the cervical sympathetic nerve, and terminate in the superior cervical ganglion. The fibers which arise here run through the Gasserian ganglion (but without joining any cells), where they unite with the first branch of the trigeminal, and run to the iris in the long ciliary nerve.

The pupils may therefore, be affected through the following mechanisms:

(A) Dilator Mechanism.	(B) Constrictor Mechanism.
1. Sympathetic center.	7. Oculomotor center.
2. Sympathetic and long ciliary nerve.	8. Oculomotor and short ciliary nerves.
3. Superior cervical ganglion.	9. Ciliary ganglion.
4. Post-ganglionic fibers.	10. Post-ganglionic fibers.
5. Endings in radial muscle.	11. Endings in sphincter muscle.
6. Fibers of radial muscle.	12. Fibers of sphincter muscle.

Stimulation of "A" causes dilatation; paralysis, constriction through the unopposed action of the constrictor mechanism.

Stimulation of "B" causes constriction; paralysis, dilatation through the unopposed action of the dilator mechanism.

The action may be located as follows (the principal drugs giving these effects are added in parenthesis):

A. It is tried whether the drug acts also when applied to the cornea, and if so, whether the effect is confined to this eye, or at least is much greater there. If this is the case, the action must be on the endings or muscle. If the drug acts only when it is introduced systemically, the action must be on the ganglia or centers. The ganglia are discussed below. *Central actions* are usually confined to the dilator center (stimulated by asphyxia, depressed in man by morphin).

B. Dilation of Pupil (Mydriasis).— The oculomotor trunk is exposed and stimulated:

1. No effect: Peripheral constrictor paralysis. It remains to distinguish between the ganglia, endings, and muscle, by stimulation of the short ciliary and of the sphincter muscle (Atropin paralyzes the oculomotor endings. What would be the result of these stimulations?)

2. Oculomotor stimulation is effective: The dilation must be due to sympathetic stimulation. The drug would be ineffective after section and degeneration of the sympathetic. Stimulation of the ganglia can be shown or excluded by section of the long ciliary (Cocain stimulates the sympathetic center, ganglion, and endings).

C. Constriction of the Pupil (Miosis).— The cervical sympathetic is stimulated:

1. No effect: sympathetic paralysis. The distinction between ganglia,

Materials Required (for entire class).— Five animals and pipettes. 2 c.c. of 1% solution of salts of atropin, physostigmin, pilocarpin, and cocain; dionin, 10%, 1 c.c.

endings, and muscle is made by stimulating the long ciliary and the radial muscle. (Nicotin paralyzes the ganglia, after a preliminary stimulation.)

2. Sympathetic stimulation is effective: The constriction must be due to oculomotor stimulation. This is generally in the endings (physostigmin, muscarin, pilocarpin). The ganglia may be excluded by section of the short ciliary; the muscle by the fact that large doses of atropin cause dilation.

The localization of these actions requires rather complicated operations; but the local effects and the antagonism can be readily demonstrated.

Experiments (To be demonstrated).—*General Method.*—Drop a few drops of the solution into the eye of the animal with a pipette. Note when the dilatation or constriction sets in—about 15 minutes (using the other eye for comparison)—when it reaches its maximum—about an hour—and when it disappears—about a day. Try whether the light reflex is preserved. Report the results, stating what conclusions are justified in each case. Cats are best adapted to the study of drugs acting on the pupil. Dogs answer very well. Rabbits can also be used, but are not quite as sensitive. It must also be remembered that in rabbits the two eyes react independently to light, so that the nose of the rabbit must be pointed to the window, if the eyes are to be compared. Rabbits do not react to Dionin.

(The excised eyes of frogs may be placed in $^1/_{10}$% solutions in normal saline, in the dark. Atropin dilates, physostigmin constricts, the iris. The results are not uniform, however.)

1. (*a*) Place a drop of *Atropin* into the eye of the animal: Dilation. The effect is confined to one eye. Light-reflex is absent. (Paralysis of oculomotor endings.)

(*b*) In an hour, drop *pilocarpin* into the same eye; little effect.

(*c*) In 15 minutes drop *physostigmin* into the same eye; constriction.

2. Into the eye of another animal, place a drop of *physostigmin:* constriction, confined to the one eye. Appears in 15 minutes, maximum in about an hour. (Stimulation of oculomotor endings.)

3. *Pilocarpin:* Drop into the eye of another animal; constriction confined to the one eye, but not as great as physostigmin. (Peripheral stimulation of the oculomotor.)

4. *Cocain:* Note the anesthesia and dilatation, confined to the one eye. The latter is not as strong as with atropin, and the pupils still react to light. (Stimulation of the sympathetic.)

5. *Dionin:* Drop some 10% solution on conjunctiva of dog or cat: hyperemia and edema.

Summarize the effects of Cocain in Chapter XXXVIII, No 14; and Dionin, No. 14A.

EXERCISE 55.—EFFECTS OF DRUGS ON (SALIVARY) GLANDS.

Explanatory.—The peripheral effects of drugs on the iris, on other forms of unstriped muscle, on the vagus mechanism of the heart, and on glands are very similar. The only important exceptions are the muscle of the arterioles and uterus, and the liver, mammary gland,

Materials Required (for entire class).—2 rabbits; hypodermic syringe. 25 c.c. of $^1/_{10}$% solution of pilocarpin; 5 c.c. of 1% atropin (the alkaloids in the form of salts); 5% acetic acid (50 c.c.).

and kidney. The action is the more typical, the more the organ is normally under nervous control.

The more important drugs act as follows:

Pure paralysis of endings: atropin.

Stimulation of endings: physostigmin, muscarin, pilocarpin. Pilocarpin also stimulates the ganglia; physostigmin the muscle and gland cells.

Ganglia: These are first somewhat stimulated, and then depressed, by nicotin, coniin, lobelia, spartein, curare, and cocain.

The glandular effects are studied most conveniently on the salivary glands. The submaxillary gland of the dog has the additional advantage that it possesses a double nerve supply. This may be utilized to prove that atropin acts on the endings and not on the gland-cells.

Glandular secretion may also be affected through centers, directly or reflexly. The salivation during apomorphin nausea (Exercise 30, No. 1) is an instance of direct central stimulation.

Experiments.— Number 1 should be tried by each student; 2 and 3 may be demonstrated.

1. **Reflex Stimulation.**— Place a little dilute acetic acid in the mouth and note the increased salivation. The inhalation of ether or chloroform acts in the same manner.

2. **Pilocarpin** (*Increase of secretions*).— Inject into a rabbit hypodermically 5 mg. (5 c. c. of 1 : 1,000) per Kg. of pilocarpin: In about half an hour, salivation occurs (stimulation of chorda-tympani, ganglion, and endings).

3. **Atropin** (Checks secretion).— Inject another animal at the same time with the same dose of pilocarpin, and when salivation is pronounced, inject 10 mg. (1 c. c. of 1%) per Kg. of atropin. On comparing the two animals in about half an hour, it is seen that the atropin checks the salivation more or less completely (paralysis of the chorda-tympani endings).

4. **Chorda Tympani Experiment** (Optional).— See Stewart's Manual, or Practical Physiology, Beddard, etc., for technic. Insert a cannula in Wharton's duct. Stimulate the cervical sympathetic: the gland becomes pale and secretes a little thick saliva. Stimulate the chorda tympani: the gland flushes and yields abundant thin saliva. Inject intravenously 30 to 40 mg. of nicotin (for a dog, or 10 mg. for a cat). Stimulation of the chorda is now ineffective, but stimulation at the hilus of the gland (*i. e.,* beyond the ganglion cells) causes secretion. The nicotin has therefore paralyzed the ganglion. Inject 10 to 14 mg. of atropin (for a dog, 5 to 15 mg. for a cat). Stimulation at the hilus causes no secretion, although the gland flushes. The atropin therefore does not act on the vasodilator endings, but it paralyzes the secretory mechanism somewhere peripheral to the ganglion. Stimulate the sympathetic: this causes secretion. The cells are therefore not paralyzed. The atropin must act on the endings. Inject some 2% pilocarpin into the duct, so that it comes in contact with the cells: secretion resumes, since the pilocarpin stimulation overcomes the atropin paralysis.

EXERCISE 56.— ANTHELMINTICS.

Study in connection with Chapter XXX.

Explanatory.— Anthelmintics are remedies used against intestinal parasites. They either kill the worms (vermicides), or narcotize them (vermifuges), so that they can be expelled by a cathartic. They are all fairly violent protoplasmic poisons, but possess a peculiar toxicity for the parasites. Aspidium and pelletierin are especially effective against tapeworm; santonin against roundworms. Quassia, iron, etc., are used by enema against threadworms.

The toxic action of these anthelmintics can be demonstrated outside of the body, by the experiments described below. The intestinal canal of the dog usually furnishes a plentiful material. These experiments can be performed in conjunction with one of the operative exercises of Chapter XXXVII.

Experiments.— Split the intestine and collect the parasites. Place some in normal saline, and some in the various anthelmintic solutions and keep at 40° C. Note that the motion ceases gradually in the anthelmintic solutions. If the worms are then promptly removed and placed in saline, they may recover.

Materials Needed.— Fresh dog's intestine; water bath at 40° C., containing bottles with 25 c. c. of 5% infusions of aspidium, quassia and spigelia; $^1/_{10}$% solution santonin, with NaOH; 1% emulsion turpentine.

CHAPTER XXXVII.

OPERATIVE WORK ON MAMMALS.

(Review the technic, pages 801 to 820, and the remarks on note-taking, page 823.)

Preliminary Remarks.— The technic of mammalian experiments is not very difficult; but it is somewhat more complicated when it is desired to utilize the material as thoroughly as possible. This may be done by employing several methods and a succession of drugs on the same animal. The economy of time and material is not the only advantage of this plan. The simultaneous registration of several functions is always useful, and often indispensable for the interpretation of the phenomena. The successive administration of drugs emphasizes their resemblance and antagonism, and the principles of therapeutics. On the other hand, this plan makes heavy demands on the attention and skill of the students. Confusion should be avoided by assigning the work in advance (see page 790). This should be studied before beginning the operation. The class may be divided into sets of six students, numbered from A to F. It is not advisable to assign less than five students to an experiment; if the class cannot be divided evenly, it is better to enlarge the sets. The student should remember that the subdivision of the work is merely for the purpose of convenience. He should be ready to co-operate with the other members of his set in their duties, and he is responsible for their work and observations, as well as for his own. Where several sets of observations are to be taken, the one on which the main stress is laid in the exercise should receive first attention, even if it should be necessary to sacrifice the others. Different experiments may be assigned to the different sets.[1] If the time is limited, it may be advisable to enlarge on this principle, and to further subdivide the exercises amongst the sets; each set doing but part of the work. The difficulty may be met more advantageously by preparing and operating the animals before the opening of the class, for a great deal of time can be wasted in this preparation. The animals should always receive the morphin a half-hour or hour before they are to be used.

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[1] The exercises may be assigned as follows (each set takes up one exercise):
First day, Exercises 58 and 59 (57).
Second day, Exercises 61, 62 and 63 (60).
Third day, Exercises 65 and 67 (64 and 66).
Fourth day, Exercise 69 to 73 (68).

There should be a demonstrator for at most two sets. He should aid in the arrangement and adjustment of the apparatus, call attention to the prominent features of the experiment, and decide when to pass from one drug to another.

The details of the experiments should be recorded in column form, as indicated in the exercises; each set keeping its own notes and diagrammatic or blue-print reproductions of the tracings. The conclusions for each drug should be briefly summarized at the end, and controlled by the results of the other sets. The demonstrators should call the attention of the class to typical or exceptional results. Every student should study all the exercises and results, including those assigned to other sets.

The apparatus needed for these experiments will be found in part in the lockers (Tables XXIII and XXIV, page 785). Further apparatus should be kept conveniently accessible to the operating table (Table XXV, page 786). The special materials (for six students) are noted at the beginning of each exercise. They should also be placed on the table. The reagents which are not in use should be arranged alphabetically on a side-shelf, as the need for them may arise at any time (Table XXVIII, page 787). The students should keep their tables and apparatus clean.

The use of small dogs will effect a considerable saving of drugs.

EXERCISE 57.—INTERPRETATION OF BLOOD PRESSURE (INTRODUCTORY).

Changes in blood pressure may be either cardiac or vascular. The pressure-tracing gives a very imperfect, and often erroneous, impression of the strength of the heart-beat. It is therefore necessary to distinguish between cardiac and vascular changes by direct experiments. The cardiac effects may be registered with the myocardiograph. They may also be deduced from the vein pressure, oncometer, or circulation time: These vary in the same direction as the arterial pressure if the changes are cardiac; in the opposite direction if they are vascular. Vascular changes may also be distinguished by direct inspection (see Exercise 51).

If the changes are cardiac it is necessary to distinguish between actions on the cardiac muscle, and on the nervous mechanisms, central and peripheral. These were discussed in Exercise 48.

Vascular changes may concern the arterial muscle, or the vasoconstrictor or vasodilator nervous mechanism. The vasodilator system is only important in a few situations, which are not sufficient to affect the general blood pressure. It is therefore only necessary to consider the vasoconstrictor nerves and the muscle.

Vasoconstriction.— The seat of the stimulation may be:

1. Central.— The drug has no effect if it is injected after destruction of the spinal cord. The venous pressure and volume of the leg increases if the drug is injected after section of the sciatic. (Strychnin, Caffein, etc.)

The stimulation may also be *reflex* (counterirritants) or from *convulsions* or *asphyxia*. These must be excluded by curare and artificial respiration.

2. Peripheral.— (The drug is effective after destruction of the spinal cord.) The stimulation may be in:

The Ganglia.— The drug does not act on excised organs. If the drug slows the stream through excised organs, the action must be either on the *endings* (suprarenal) or on the *muscle fibers* (barium). The distinction between these is not easy. If the endings alone are affected, the drug will not act on every organ, and it will fail to act after apocodein, or after the organ has been excised for some hours. If the effect is on the muscle, it can be obtained in all organs, and for many hours after removal from the body, and after apocodein.

Simultaneous Action at Several Points.— The above experiments indicate only the most peripheral structure on which the drug acts. If it affects a peripheral structure and the center simultaneously, a positive distinction is possible only by maintaining a separate artificial circulation through the center. By this means it has been shown that nitrites paralyze the vasoconstrictor mechanism both centrally and peripherally. These experiments, however, are so complicated that they are open to fallacies.

Vasodilation.— The paralysis may be:

1. Central— Stimulation of the peripheral end of the splanchnic nerve raises the blood pressure; asphyxia, or central stimulation of the sciatic or of the cardiac depressor does not alter the blood pressure. The paralysis may be *direct* (Chloral, Chloroform) or *reflex* (depressor stimulation, shock), or the result of extreme asphyxia or anemia. These must be excluded.

2. Peripheral.— Stimulation of the splanchnic is ineffective. Paralysis of the *ganglia* (as by nicotin) is excluded by stimulating beyond them. If this is still effective, the action must be on the endings, muscle, or capillaries. If it is on the *endings,* the effect of suprarenal will be abolished or diminished, but barium will still be effective. Paralysis of the endings is produced by nitrites (probably), apocodein, large doses of ergot, etc. If the *muscle* is paralyzed, even barium will fail to produce a rise.

With arsenic, and some other metals, there is a fall of pressure, of vascular origin, but the vasomotor mechanism responds well to direct or reflex stimulation. Their action is on the capillary-walls. *Capillary paralysis* is also characterized by greater permeability — intravenous injection of salt-solution leading readily to muscular edema (Magnus, 1899).

EXERCISE 58.— EFFECTS OF ANESTHETICS ON BLOOD PRESSURE AND RESPIRATION.

Study in connection with Chapter XIX.

This exercise has the purpose of demonstrating the ordinary phenomena and accidents of anesthesia, and their treatment.

Special Materials Needed.— Dog (not morphinized). Water bath with large bottles of normal saline at 40° C.

Chloroform (50 c. c.); Adrenalin, 1 : 1,000 (2 c. c.).

Distribution of Work.— (See page 790).

Students A and B take place I; C and D = II; E and F = III (respiratory tracing and rate). E and F may also do the anthelmintic experiments (Exercise 56).

Observations Required.—

Date: Animal: Age:

Weight: Sex: Abnormalities:

Record the results in column-form, as follows (the numbers in parenthesis refer to the place to which these observations are assigned):

TIME.	DRUG.	DOSE per Kg.	STRENGTH OF SOLUTION.	Manner of Injection.[1]	HEART Rate, Regularity, and Strength.
(I)	(I)	(I)	(I)	(I)	(II)

BLOOD PRESSURE.					
Mean Height.	Pulse Pressure.	Respir.[2] Variations.	Tracing Number of	RESPIRATION Rate, Strength, Tracing Number.	REMARKS.
	(II)			(III)	(III)

Conclusions from individual experiment:

Conclusions from class-work:

[1] Hypodermic .. H; Intravenous = V.
[2] Whether moderate, weak, or exaggerated.

The principal stress should be laid on the blood pressure tracing and the direct observation of the respiration. The respiratory tracing must not be allowed to interfere with other observations.

Experiments.— (Arrange the apparatus for the blood pressure and respiratory tracings and the injection burette.)

1. Preliminary Observations.— Make a set of observations on the normal animal (which should be quietened as much as possible). (Note that the heart is markedly faster in inspiration than in expiration — the blood pressure is also higher in inspiration.)

2. Ether Anesthesia.— Pour a tablespoonful of ether on a sponge, fold over this a towel in several layers, and apply it closely to the mouth of the dog, excluding the air.[1]

Notice that there is considerable struggling at first; the animal then becomes quiet, and the legs drop limp if they are lifted; the cornea remains sensitive. Tie the dog to the board. Insert the cannulæ into the trachea, and into the central end of the carotid artery, and femoral vein (see page 807). Give ether by Woulf's bottle. Connect for blood pressure and respiratory tracings. Take normal tracings and a set of observations: The typical ether anesthesia shows a slowed and shallow respiration (depression of respiratory center): moderate fall of blood pressure (depression of vasomotor center): and quickened heart (depression of vagus center) with practically undiminished strength of beats (Fig. 82C, page 430). Expose the vagus (see page 808) and sciatic (see page 809).

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[1] The anesthetizer should not withdraw his attention from his work throughout the experiment. He should watch the respiration and heart closely, and remove the anesthetic with the first sign of failure of these functions. If the respiration is rapid, the anesthetic must be lessened.

(*Numbers 2 and 3 may be omitted if they have been performed satisfactorily in the physiology course.*)

3. **Stimulate the vagus** with weak tetanizing shocks, taking tracings and observations: The heart is slowed, the pressure falling in consequence. The respiration is increased. Strengthen the current: the heart is arrested, the pressure falling further. The respiration stops in the inspiratory phase. Let the animal return to normal.

4. **Stimulate the Sciatic.**— The respiration is considerably increased, and the blood pressure rises (stimulation of the respiratory and vasomotor centers).

5. **Chloroform.**— Take a set of observations. Let the animal inhale chloroform. Note that the respiration, pressure, and strength of heart are diminished (Fig. 82, page 430), whilst the heart rate is often increased (depression of the respiratory, vasomotor and vagus centers, and cardiac muscle). Push the chloroform until the respiration stops; the pressure and heart are low.[1] Stimulate the central end of the sciatic or let the animal inhale some ammonia. This may revive respiration (*reflex stimulation*). If it is not effective, proceed quickly to the next number.

6. Perform *artificial respiration.* Note that the blood pressure can be altered at will by changing the efficiency of the respiration.

7. **Resuscitation, Cardiac Massage.**— Discontinue the artificial respiration, and administer chloroform until *the heart stops* (Fig. 81, page 429). Begin at once artificial respiration, together with cardiac massage, *i e.*, with strong, rapid, *rhythmic compression of the thorax* (rate of at least 80 per minute). This must be done very vigorously. Observe on the tracing that an artificial circulation can be kept up in this manner. If the animal does not revive in two minutes, continue the procedure, but inject at the same time into the vein 1 c. c. of 1 : 1,000 *adrenalin* in 50 c. c. of warm saline. The animal will probably revive, since the suprarenal raises the blood pressure by stimulating the heart and the blood vessels (Figs. 62, page 289, and 64, page 290).

8. **Asphyxia.**— If the animal survives withdraw the anesthetic (using artificial respiration as long as necessary) until the anesthesia is but slight. Study the effects of *asphyxia* by tying the trachea: The respiration, especially the inspiratory efforts, will first be increased (dyspnea, stimulation of the respiratory center); then it will be lessened, with rare, gasping, powerful respiratory efforts (depression of center); the blood pressure (Fig. 47, page 151) will rise during the dyspnea (stimulation of vasomotor center), and will then fall; the heart rate is greatly slowed, with typical strong vagus beats (stimulation of vagus center). During the dyspnea, the animal makes convulsive movements and the pupils dilate (stimulation of the corresponding centers). The pupils contract again when the paralysis occurs.

9. **Apnea.**—Keep up a brisk artificial respiration for a few minutes. Stop suddenly, and observe that the animal does not breathe for some time, the circulation being good. This *apnea* is due to the fact that there is not enough CO_2 in the blood to stimulate the respiratory center to its rhythmic activity.

10. **Death by Chloroform.**— Kill the animal by chloroform, taking tracing. See that respiration stops before the heart.

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[1] The immediate cause of death in chloroform anesthesia is usually failure of respiration; but if the vapor is very concentrated, death may occur before the anesthesia is complete, through stoppage of the heart, by a tregeminus-vagus reflex; or by direct paralysis of the cardiac muscle (Fig. 81, page 429).

Excise the suprarenals, cut them up, and place in 10 c. c. of 50% glycerin for future use.

Excise the intestines and split open and collect the parasites and perform Exercise 56.

Summarize the effects of asphyxia and carbon-monoxid, Chapter XXXVIII, No. 15.

EXERCISE 59.—EFFECTS OF DRUGS ON THE CIRCULATION (VASOMOTOR).

Special Materials Needed:

Morphinized dog.
Stephen Hale's Manometer (see page 815).
Amyl Nitrite (5 c. c.); Adrenalin, 1 : 1,000 (·5 c. c.); Ergot, 2% (25 c. c.); Hydrastis, 2%, filtered (15 c. c.); Hydrastinin hydrochlorid, $^1/_{10}$% (15 c. c.); Aconite, 10% (5 c. c.); Phenol, 1% (50 c. c.); Sodium Sulphate, 2% of dried (400 c. c.); Strychnin salt, $^1/_{100}$% (10 c. c.); $^1/_{10}$% (·10 c. c.).

Distribution of Work (see page 790):

Students C and D take place I; E and F = II; A and B = III. Observation of respiration; myocardiogram, oncometer, or vein-manometer (one of these being assigned to each set).

Observations Required:

Date: Animal: Age:
Weight: Sex: Abnormalities:

					Blood Pressure.			
Time.	Drug.	Dose per Kg.	Strength of Solution.	Manner of Injection.	Mean Height.	Pulse Pressure.	Respir. Variations.	Trac. No.
(I)					(II)			

Heart Rate, Regularity, Trac. No. and Strength.	Vein-Pressure.	Oncometer.	Respiration. Rate, Strength.	Remarks.
(II)	III		(III)	(III)

Conclusions from individual experiments:

Conclusions from class-work:

The principal stress lies on the blood pressure tracing, and the other experiments must not be permitted to interfere with this.

Preliminary Operations.—Arrange for carotid tracing and for myocardiogram, vein-pressure, or oncometer. Weigh the dog. Anesthetize. Insert cannulæ into trachea and central end of carotid artery and femoral vein (both veins, if the vein-pressure is to be taken). (Expose the kidney, spleen, or intestine — if oncometer is to be used; see page 817.) Connect for tracings and intravenous injection.* Make preliminary observations and take normal tracings.

Experiments.— One of the sets should make experiments 1 and 2 with the Stephen Hale manometer (page 815), then continue with mercurial manometer and tracings.

1. **Amyl Nitrite.**—(Fig. 83, page 472; see Chapter XXI.)

Let the dog inhale a little Amyl Nitrite through the tracheal cannula. Considerable fall of blood pressure and increase of vein-pressure and oncometer (vasomotor paralysis); and some quickening of the pulse (vagus depression). Respiration usually increased. The effects pass off rapidly when the administration is discontinued. Other nitrites and nitroglycerin produce similar effects.

If the vagus was depressed before the nitrite was given — as denoted by fast pulse — there may not be any further quickening.

2. **Suprarenal** (Fig. 62, page 289; Chapter XIII).— Inject the suprarenal solution intravenously (either the solution prepared in the preceding experiment or adrenalin (½ c.c. per Kg. of 1/1000%). Rise in blood pressure and fall in vein-pressure and oncometer (peripheral vasoconstriction); slower pulse (vagus stimulation) and stronger heart (stimulation cardiac muscle); respiration usually increased (higher blood pressure?). Cardiac slowing often precedes the vasoconstriction. Note that the effects disappear rapidly.

Not to be Done by Class.— The slowing disappears largely on dividing the vagi (hence stimulation is central); the rise of pressure occurs after section of cord (hence peripheral); the action disappears as rapidly if the ureters are tied (not due to rapid excretion); the action reappears if a further dose is administered (hence not fatigue, but destruction of the poison).

The even sets proceed with No. 3; the odd sets with 3a or 3b. All sets continue with No. 4 to the end.

3. **Ergot** (Fig. 90, page 502; Chapter XXIII).—*Intravenous injection.*— Inject intravenously 0.04 Gm. × Kg. (2 c.c. × Kg. of 2%) fluidextract of ergot: Sudden and large fall of blood pressure, followed by prompt recovery and generally a slight and short rise above normal.

During the fall, the heart is weakened and quickened, and the oncometer is diminished. The fall is therefore due to weakening of the heart. During the rise, the heart is strengthened; the oncometer may increase or remain stationary. The rise is consequently due to strengthening of the heart, with some vasoconstriction.

During the fall the heart is quickened and the respiration increased. This is due to the low blood pressure. The cardiac effects can be reproduced on excised hearts and are therefore direct actions.

The fall of pressure is not seen when the ergot is injected subcutaneously or into the muscles.

3a. **Hydrastis.**— (Therapeutic dose): Inject intravenously 0.02 Gm × Kg. (1 c.c. × Kg. of 2%, filtered). Short fall of pressure, followed by persistent rise. Both phenomena are in part cardiac, in part vascular. The oncometer results are therefore variable.

3b. **Hydrastinin.**— (Therapeutic dose): Inject intravenously 1 mg. × Kg. (1 c.c. × Kg. of 1/10%) of the hydrochlorid: Rise of pressure and increased strength of heart.

4. **Aconite (Therapeutic Dose).**—Inject into vein a therapeutic dose of aconite, 0.015 Gm. per Kg. (0.15 c.c. per Kg. of 10% tincture): Slight slowing of the heart (stimulation of vagus centers) or no effect. Respiration increased (stimulation of center).

The sets with odd numbers will proceed to numbers 5 and 6; those with even numbers to 7 and 8. All will remove the suprarenals (9). All accessory apparatus should be removed, and the animal board put on a separate table (so that the convulsions will not jar the drum).

5. Carbolic Acid (Fig. 78, page 361; Chapter XVII).—Inject into vein a *toxic dose of Phenol,* 50 mg. per Kg. (5 c. c. per Kg. of 1%): Collapse: Pressure falls (vasomotor and cardiac paralysis: beats fast and small (cardiac depression); respiration lessened (depression of center); convulsive (stimulation spinal cord). Try to observe effect of convulsions on blood pressure (rise). When the pressure has fallen low (repeating ½ the dose in 10 minutes if necessary) inject quickly into vein.

6. Sodium Sulphate, 50 c. c. per Kg. of 2% (dried).—The functions may return rapidly to normal (stimulation).

7. Strychnin (Fig. 46, page 149; Chapter VIII).—Inject hypodermically the *therapeutic dose of strychnin sulphate,* 0.07 mg. per Kg. (0.7 c. c. of 1/100%): some increase of respiration (central stimulation) (Fig. 46, D); circulation little changed.

8. Inject hypodermically the *tetanic dose of strychnin sulphate,* 0.25 mg. per Kg. (¼ c. c. per Kg. of 1/10%). If no tetanus occurs in 15 minutes repeat one-half this dose. (The dose which is advised is tetanic in normal dogs, but the effect may be diminished by the anesthesia.) Before the onset of the tetanus, the respiration is increased, but the circulation is little altered. With the sudden onset of the tetanus, the pressure rises abruptly (central vasomotor stimulation), and then falls with the cessation of the spasm, to a point considerably below normal (central vasomotor depression); the heart is quick during the spasm (inhibition of vagus); slow and strong after (vagus stimulation). The respiration is rapid during the tetanus, depressed in the intervals. Note that the spasms can be brought on by jarring the table, or by blowing on the animal. The spasms become successively weaker, and the blood pressure does not rise so high (depression of the convulsive and vasomotor centers). The heart remains rapid (depression of vagus center) but strong. The respiration ceases (paralysis of the center), and the pressure falls. Begin artificial respiration at once: the animal can be kept alive almost indefinitely. The heart and respiration remain fairly good. Note that the pressure varies with the efficiency of the artificial respiration. Let the animal die. Note the early onset of rigor (due to tetanus).

9. If the anthelmintics were unsatisfactory in the preceding experiment, they may be repeated. Excise the suprarenals, cut them up, and extract with 10 c. c. of 50% glycerin, for future experiments.

Summarize the effects of ergot and phenol in Chapter XXXVIII, Nos. 16 and 17; hydrastis and hydrastinin, Nos. 17a and b.

EXERCISE 60.—CHANGES IN RESPIRATION (INTRODUCTORY).

I. Stimulation of the Respiratory Center may be due to:

(A) Insufficient Oxidation of the Blood:

1. Through mechanical hindrance: The volume of air does not correspond to the violence of the effort. The obstruction may be by:

(*a*) *Mucus:* Râles.

(Pilocarpin.)

(*b*) *Constriction of the bronchial muscles.* The latter may be *direct* or *reflex.* Reflex stimulation would be abolished by section of the vagi.

2. Through changes in the circulation: inefficient work of the heart or vasodilatation.

(Cardiac depressants.)

3. Through chemic changes:

(*a*) *In the blood* (as Methemoglobin formation, cyanids, etc.).

(*b*) *Increased tissue waste:* Increased CO_2 and N excretion.

(Hyperpyrexia.)

(B) Reflexly from Pain or Convulsions.

(Strychnin.)

(C) Direct Stimulation by the drug: shown by exclusion of the above. The respiratory reflexes are unusually active.

(Strychnin, Caffein, Ammonia.)

II. Diminished Respiration may be from:

(A) Paralysis of the Muscles or Endings: Stimulation of the muscle or of the phrenics not effectual.

(Curare.)

(B) Apnea: disappears in a short time.

(C) Paralysis of the Center:

1. Through Anemia: Disappears if the aorta is clamped.

(Nitrites.)

2. Direct: Through exclusion. The paralysis may be *primary* (Ether), or it may be *secondary* to asphyxia; *i. e.,* preceded by dyspnea (CO).

3. Reflexly: Irritant vapors.

(Ammonia.)

EXERCISE 61.—EFFECTS OF DRUGS ON RESPIRATION.

Special Materials Needed:

Rabbit.

Feeding-tube and bulb; pneumograph (gas meter).

Urethane, 20% (10 c.c.); Ammonia water (5 c.c.); Caffein 1% (10 c.c.); Heroin hydrochlorid, $^1/_{10}$% (5 c.c.); Morphin salt, 1% (5 c.c.); Atropin sulphate, 1% (5 c.c.); Strychnin salt, $^1/_{100}$% (10 c.c.); $^1/_{10}$% (20 c.c.).

Distribution of Work (see page 790):

Students E and F = place I; A and B = respiratory tracing; C and D = place III.

The different sets may employ different recording methods; but it is essential that the trachea is left intact for No. 2; while No. 9 should be taken from the tracheal cannula.

One of the sets may take pneumograms from a non-anesthetized rabbit (see page 000), using drug Nos. 2 to 7.

Another set may measure the volume of the expired air with a gas-meter, instead of taking tracings. The animal is anesthetized, and the tracheal cannula connected with the meter, interposing a valve to separate the inspired and expired air. A reading should be taken every five minutes. The drugs 3, 5, 6, and 7 may be used in succession.

Observations Required:

Date: Animal: Age:

Weight: Sex: Abnormalities:

TIME.	DRUG.	DOSE per Kg.	STRENGTH OF SOLUTION.	Manner of Injection.

(I)

RESPIRATION. Rate, Strength, Trac. No. (II)	REMARKS. (III)

Conclusions from individual experiments:	Conclusions from class-work:

Pulse and pupils when asked for. If the respiration stops, note whether this is in the inspiratory or expiratory phase.

Preliminary Operations.— Arrange for respiratory tracing. Weigh the animal. Administer 0.75 Gm. of urethane (3.5 c.c. of 20%) per Kg. by rectum (see page 804). Complete anesthesia in fifteen minutes by ether, if absolutely necessary. Expose sciatic and vagus (see page 809). The sciatic is only needed if No. 1 is to be done. Connect for respiratory tracing. Take normal rate and tracing.

Experiments.— **1.** Take preliminary tracing. *Stimulate the vagus and the sciatic*[1] with weak and strong tetanizing shocks, taking tracings and observing whether the heart is markedly slowed. (Compare page 913.)

2. Ammonia Inhalation.— (Chapter XXVIII).— Let the animal inhale ammonia. Notice respiratory standstill and stoppage of the heart (reflex stimulation of vagus center by irritation of the trigeminal endings). If the animal is not too deeply anesthetized, it will partly recover and struggle. On removing the ammonia the respiration is increased (dyspnea) and the heart resumes. Perform tracheotomy.

The even sets will do Experiments 3 and 4, the odd sets 5 and 6. All sets will proceed with Experiment 7 to the end.

3. Caffein (Figs. 48, page 163, and 50, page 165; Chapter VIII).— Inject hypodermically 30 mg. per Kg. of Caffein (3 c.c. per Kg. of 1%): The respiration increases and the animal may come partly out of the anesthetic (stimulation of the respiratory and other centers).

4. Heroin (Chapter IX).— Inject hypodermically 0.5 mg. per Kg. of Heroin hydrochlorid (0.5 c.c. per Kg. of $^1/_{10}$% solution). The rate of respiration is slowed, but the inspiratory excursion is increased (peculiar depression of the excitability of the respiratory center).

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[1] This may be omitted if the experiment has been performed satisfactorily in the Physiology Course.

5. **Morphin** (Chapter IX).—Inject hypodermically 10 mg. per Kg. of Morphin sulphate (1 c.c. per Kg. of 1%). Respiration becomes slow and shallow (depression of respiratory centers).

6. **Atropin** (Fig. 55C, page 230; Chapter XI).—Note the pupils. See that stimulation of vagus slows the heart. Inject hypodermically 5 mg. per Kg. of Atropin sulphate (½ c.c. per Kg. of 1%). Rate and strength of respiration increased (stimulation of respiratory center—antagonism to morphin). The pupil dilates (paralysis of oculomotor endings). Stimulate the vagus: The heart is not slowed (paralysis of the vagus endings).

7. **Strychnin** (Fig. 46D, page 149; Chapter VIII).—Inject hypodermically 0.2 mg. per Kg. of *strychnin* sulphate—therapeutic dose (2 c.c. per Kg. of $^1/_{100}$%): Increased respiration (stimulation of respiratory center). Reflexes increased (increased excitability of spinal cord).

8. **Convulsive and Tetanic Doses of Strychnin.**—(Take respiratory tracing from the trachea.) After ten minutes inject 0.5 mg. per Kg. of strychnin (½ c.c. per Kg. of $^1/_{10}$%), and repeat every five minutes until death. In the convulsive stage (*i. e.*, before the tetanus is complete) the respiration is markedly increased. It is fixed during the tetanus, depressed between the spasms. It stops before the heart. Notice the asphyxial dilatation of the pupils.

In non-anesthetized rabbits, the convulsive dose of strychnin is 0.3 mg. per Kg.; the tetanic dose, 0.4 mg.; the just fatal dose, 0.57 mg. per Kg. A much larger quantity is required after urethane (how many times larger, in your experience?).

9. Notice the early onset of the *rigor mortis.* Excise the suprarenals, cut them up, and place in 10 c.c. of 50% glycerin.

Summarize the effects of Ammonia and Morphin in Chapter XXXVIII, Nos. 18 and 19.

EXERCISE 62.—CIRCULATION AND RESPIRATION (DIGITALIS)

Special Materials Needed:

Morphinized dog; water bath.
Warm Normal Saline (400 c.c.); Ammonium Chlorid, 1% (200 c.c.); Litmus paper; Digitalis, fresh 4% infusion (50 c.c.); Strophanthus, $^1/_{10}$% (50 c.c.); Caffein, 1% (10 c.c.).

Distribution of Work (see page 790).

Students A and B = place I; C and D = II; E and F = III: respiratory tracing or oncometer in Nos. 1 and 2; myocardiogram or oncometer in 3 and 4.

Observations Required:

Date:	Animal:	Age:
Weight:	Sex:	Abnormalities:

					BLOOD PRESSURE.			
TIME.	DRUG.	DOSE per Kg.	STRENGTH OF SOLUTION.	Manner of Injection.	Mean Height.	Pulse-Pressure.	Respir. Variations.	Tracing Number.

(I) (II)

HEART Rate, Regularity, Trac. No., and Strength.	Oncometer.	RESPIRATION. Rate, Strength, Trac. No.	REMARKS.

(III)

Conclusions from individual experiments:	Conclusions from class-work:

The main stress should be laid on the blood-pressure tracing.

Preliminary Operations.— Arrange for blood pressure and myocardiac tracing, also respiratory tracing or oncometer. Weigh and anesthetize the animal. Insert cannulæ into the trachea, carotid artery, and femoral vein (central end). (Expose kidney, spleen, or intestine for oncometer, if desired; small incision). Connect for tracings. Take normal observations and tracings.

Experiments.— 1. Saline Injection.— *Blood pressure* (Respiration or oncometer).—(Chapter XXIV.)— Take a normal tracing. Inject intravenously 25 c. c. per Kg. of warm Normal Saline. Rise of blood pressure, stronger and usually slower heart, increased oncometer and respiration. The effect is usually short, and may be small, especially if the animal is in good condition. (Stimulation of the medullary centers and cardiac muscle by the increased quantity of blood, and by salt action.) Exceptionally, the results may resemble those of ergot, Exercise 59. No. 3.

2. Ammonium Chlorid.—*Blood pressure* (Respiration or oncometer).— (Fig. 92, page 559; Chapter XXV.) — Inject intravenously 0.15 Gm. per Kg. of Ammonium chlorid (15 c. c. per Kg. of 1%): Rate and force of respiration increased, blood pressure rises; heart variable (stimulation of medullary centers). Respiratory excursions increased (heightened excitability of vagus center). Hold moist red litmus paper over respiration tube; it is not blued (ammonia is not excreted by lungs). The ammonia effect is quite short (rapid elimination and destruction).

Connect for myocardiogram (page 559).

Most of the sets do Experiments 3 and 5; a few do 4 and 5.

3. **Digitalis.**—*Blood pressure* (Myocardiogram)[1] (Figs. 85 and 86. pages 480 and 481, Chapter XXII.)—When the conditions have returned to normal, inject intravenously 0.04 Gm. per Kg. of digitalis (1 c.c. per Kg. of fresh 4% infusion). *Therapeutic stage of digitalis action:* Heart slowed, beats stronger (stimulation of cardiac muscle and vagus); blood pressure high (cardiac effect and vasomotor stimulation; respiration increased (stimulation of center) (Fig. 85, *b,* and *c.*; Fig. 86, *b*). When this action has been observed (waiting 20 minutes if necessary), repeat the injection every fifteen minutes until death: *Toxic stage of Digitalis.* The effects of toxic doses of digitalis on the circulation (Fig. 85, *d,* and Fig. 86) are extremely irregular, and may vary from moment to moment. The rate is generally increased, but may be slowed at times. The irregularities usually occur in groups (see the figures); these are partly due to the influence of respiration (the reflex excitability of the vagus being heightened), partly to arhythmia of the auricles and ventricles. The effects are based on an increased excitability of the cardiac muscle with systolic tendency (consult Exercise 48), and on irregular activity of the vagus. Death occurs suddenly, sometimes by vagus stimulation, as in Fig. 85, but more commonly by delirium cordis, the result of over-stimulation of the heart. The blood pressure may remain high until the end, or it may fall, according to the output of the heart and the persistence of the vasoconstriction.

4. **Strophanthus.**—*Blood pressure* (Myocardiogram).—The effects correspond to those of digitalis (3), except that the vasoconstriction is relatively less prominent. Inject 0.0015 Gm. per Kg. (1.5 c.c. per Kg. of 1 : 1,000) and repeat as with digitalis.

5. **Caffein Rigor** (Chapter VIII).—Inject 10 c.c. of 1% caffein into the peripheral end of the femoral artery. Observe that this leg goes into rigor before the other (*drug rigor*).

Excise the suprarenals and place in 10 c.c. of 50% glycerin.

Summarize the effects of Ammonium Chlorid in Chapter XXXVIII, No. 20.

EXERCISE 63.—EFFECTS OF DRUGS ON HEART AND BLOOD PRESSURE.

Review Exercise 48.

Special Materials Needed:

Morphinized dog.

Sodium chlorid, 1% (50 c.c.); Magnesium sulphate, 3.6% of the salt dried at 110° C. (50 c.c.); ½% of Curare (20 c.c.); Strychnin salt, $^1/_{100}$% (5 c.c.); Caffein salt, 1% (25 c.c.); Potassium Chlorid, 1% (50 c.c.); Adrenalin, $^1/_{10}$% (2 c.c.); Aconite, 10% (50 c.c.); Veratrin 1% (25 c.c.).

Distribution of Work (see page 790):

Students C and D = place I; E and F = II, absorption, stimulation; A and B = III (myocardiogram, observation of respiration).

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[1] Use a *very* slow drum for the blood pressure, and a more rapid speed for the myocardiogram.

Observations Required:

Date: Animal: Age:

Weight: Sex: Abnormalities:

TIME.	DRUG.	DOSE per Kg.	STRENGTH OF SOLUTION.	Manner of Injection.	HEART Rate, Regularity, Trac. No., and Strength.
		(I)			(III)

BLOOD PRESSURE				RESPIRATION Rate, Strength, Trac. No.	REMARKS.
Mean Height.	Pulse Pressure.	Respir. Variations.	Trac. No.		
	(II)			(III)	

Conclusions from individual experiments.

Conclusions from class-work:

The main stress should be laid on the myocardiogram. The blood pressure tracing should be taken with a very slow speed; the myocardiogram somewhat faster.

Preliminary Operations.—Arrange for myocardiogram and blood pressure tracing. Weigh and anesthetize the animal. Insert cannulæ into trachea and central end of carotid, and femoral vein. Connect for intravenous injection.

Experiments.— 1. Absorption of Sodium Chlorid and Magnesium Sulphate (Chapter XXIV).— Make a 2-inch incision in linea alba, draw out a loop of intestine, and ligature it in two places, about 25 c.m. apart. Make an opening just inside one of the ligatures. Strip the piece of intestine of its contents, insert the end of a funnel into the opening, and allow a measured quantity of $MgSO_4$ solution (3.6% of the salt dried at 110° C.) to flow in. Withdraw the funnel and tie off the opened portion. Replace the loop of intestine and draw forth another loop; treat this loop also, using 1% NaCl instead of $MgSO_4$, and sew up the wound. The NaCl and $MgSO_4$ solutions have the same freezing point. Leave until all the other experiments are finished, then proceed by No. 9.

Connect for blood pressure tracing and take normal observations and tracing.

2. Curare.— *Motor Excitability, Blood Pressure.*—(Fig. 58, page 256, Chapter XII.) — Take normal tracing. Inject into femoral vein 1 c.c. per Kg. of ½% Curare every ten minutes until the respiration becomes very weak (depression of nerve endings in striped muscle). Counterirritation (whipping with towel wetted with cold water) or stimulation of sciatic still causes feeble respiratory efforts; sciatic stimulation also causes weak contraction of leg (the excitability would disappear completely if larger doses of curare were used).

The effects on the circulation are shown in the figure.

Start artificial respiration and connect for myocardiogram (page 818). Take normal tracings.

The odd sets proceed with 3, 4, and 7, the even sets with 5, 6, and 8. All sets do 9.

3. **Strychnin** (Therapeutic Dose).—*Myocardiogram,* Blood pressure (Chapter VIII).—Inject a therapeutic dose of strychnin (0.04 mg. per Kg.) into the vein (0.4 c.c. per Kg. of $^1/_{100}$%): No effect (therapeutic doses of strychnin do not stimulate the heart).

4. **Caffein.**—*Myocardiogram,* Blood pressure (Fig. 50, page 165; Chapter VIII).—In five minutes inject into the vein a therapeutic dose of caffein (20 mg. per Kg., 2 c.c. per Kg. of 1%): Increase in strength and rate (stimulation of myocardium).

5. **Potassium Chlorid.**—*Myocardiogram,* Blood pressure (Fig. 91, page 557; Chapter XXV).—Inject 1 c.c. per Kg. of 1% KCl intravenously every ten minutes: the heart will be somewhat weakened, slowed, and irregular (the pressure falling) and will stop rather suddenly. (Paralysis of cardiac muscle.) (Magnesium produces similar effects.)

6. **Suprarenal.**—*Myocardiogram,* Blood pressure (Chapter XIII).—Inject at once some suprarenal intravenously (1 c.c. per Kg. of extract or 0.2 c.c. per Kg. of 1 : 1,000 adrenalin. each in 25 c.c. of warm normal saline): the heart recovers and beats with strong slow beats (stimulation of vagus and myocardium).

7. **Aconite** (Fatal Dose).—*Myocardiogram,* Blood pressure (Fig. 66, page 318; Chapter XV).—Inject intravenously a *fatal dose of* Aconite (0.1 Gm. per Kg., 1 c.c. per Kg of 10%): The heart is first slowed and strengthened (stimulation of vagus and myocardium); then weak and rapid (paralysis of vagus); then very irregular (overstimulation of myocardium); goes into delirium cordis and stops. The action may require half an hour.

8. **Veratrin.**—*Myocardiogram,* Blood pressure (Chapter XV).—Inject 10 mg. per Kg. (1 c.c. per Kg. of 1%): (Effects similar to aconite (No. 7) and to digitalis (Exercise 62, No. 3).

9. Open the abdomen, find the ligated intestines, and measure their contents: The $MgSO_4$ has not diminished as much as the NaCl, because the former salt is not readily absorbed, and retains water by salt action.

Excise the suprarenals, cut them up, and preserve in 10 c.c. of 50% glycerin.

Summarize the effects of Aconite, Veratrin, Curare, and Magnesium, in Chapter XXXVIII, Nos. 21, 22, 26, and 26a.

EXERCISE 64.—EFFECTS OF DRUGS ON THE KIDNEY (INTRODUCTORY).

The physiology and pharmacology of the kidneys differ conspicuously from that of the typical glands, such as the salivary: The kidney is not markedly affected by the usual glandular stimulants and depressants, such as pilocarpin and atropin. It functionates quite well when the nervous connections are divided. Its activity is most intimately connected with the state of the circulation. It will be seen in Exercise 69 that the *quantity of urine* is influenced mainly by the filtration pressure, *i. e.,* the difference between the pressure in the glomerular capillaries and in Bowman's capsule. This is determined by the systemic circulation, by the state of the vessels within the kidney, and by the viscidity of the blood. There is evidence that the kidneys possess an active vasodilator as well as a constrictor mechanism. The *composition of the urine* cannot be explained by a simple filtration theory. It necessitates the acceptance of unexplained forces. The changes occur by reabsorption, and also by secretion.

The mechanism of urine-secretion may be explained by several alternative theories, none of which is positively established to the definite exclusion of the others. The following working theory furnishes the most simple explanation of the phenomena: A physical filtration of urine occurs in the glomeruli. The filtrate probably corresponds to a proteid-free plasma. The quantity of the filtrate depends mainly on the filtration pressure.

During the passage of the glomerular fluid through the urinary tubules, a series of changes occur, by the operation of powerful forces which cannot yet be explained on a physical basis. These cause the reabsorption of certain constituents and the secretion of others. The extent of these changes is indicated by the departure of the composition of the final urine from that of the proteid-free blood plasma. It varies inversely to the rate of urine flow (a more rapid flow leaving less time for these changes). It is also influenced by the composition of the blood, but in a manner which is not fully understood.

The absorption involves mainly the water and chlorids, to a less extent the sulphates and phosphates; urea being the least absorbable constituent.

The secretion bears on the uric acid, certain pigments, and probably a variable proportion of the urea and of other urinary constituents.

Diuretics (drugs which increase the urine flow) may be grouped into the following classes:

Digitalis.— Acts by increasing the filtration pressure, through increased output of the heart, with stronger pulse-pressure; through lessened venous pressure; through the absorption of effusions, producing hydremic plethora. The diuretic tendency is counteracted by constriction of the renal arterioles. It is therefore but little diuretic in health, but strongly so in cardiac disease, where the conditions for its favorable action are present.

Irritant Diuretics.— Volatile oils, calomel, alcohol, etc.; probably some of the salts, acids, and alkalies: Small doses increase the vascularity and thereby the filtration pressure. It is possible that they also stimulate the secreting cells. Larger doses cause stasis and injury to the cells, and consequently lessened output of urine, with albuminuria, casts, and eventually anuria. Consult Exercise 33.

Irritant diuretics should not be used in nephritis.

Saline Diuretics, including all substances which act by salt-action (water, non-toxic salt solutions, glucose, urea, etc.).— These produce "*hydremic plethora,*" *i. e.,* they dilute the blood. This increases the filtration pressure by increasing the total quantity of fluid; by lessening the viscidity and thereby reducing friction in the arterioles and capillaries; the lessened viscidity also reduces the filtration resistance. Stronger solutions further increase the filtration pressure by osmotic shrinkage of the renal cells. It is possible that some of these substances also stimulate the secreting cells or depress the reabsorption.

Stimulant Diuretics [Caffein, Theobromin, Theophyllin (Theocin).] — These act directly on the kidney. They cause some dilation of the vessels, probably by shrinking the cells, and thereby increase the filtration pressure; but this is not the essential cause of the diuresis. This is thought by some to consist in a depression of the reabsorbing function; but it is more likely that they act by stimulating the secretory cells.

[Drugs which constrict the vessels (suprarenal, barium, etc.) lessen the output of urine, the resistance in the afferent arterioles being increased more than the general blood pressure. The effect of vasodilators is variable, according to whether they act more powerfully on the systemic or on the local vessels. In excised kidneys, vasoconstrictor drugs always lessen the urine flow, whilst vasodilators (cyanids) increase it.]

Consult Exercises 68 to 72.

EXERCISE 65.—EXPERIMENTS ON DIURESIS (INTACT KIDNEYS).

Read Exercise 64.

Special Materials Needed:

Morphinized dog.

Two ureter cannulæ. Water bath at 40° C. Large porcelain capsule; glass rods; large funnel, muslin strainer, and beaker.

Warm Sodium sulphate, 2.5% of dried crystals (250 c.c.); Silver nitrate solution; HNO_3; Diuretin, Agurin, or Theocin, 5% (10 c.c.); warm normal saline (250 c.c.); Barium chlorid, 1% (20 c.c.); Chloroform (10 c.c.).

Distribution of Work (see page 790):

Students E and F take place I (also oncometer, if desired); A and B = II; C and D = III (ureter flow; observation of respiration).

Observations Required:

Date: Animal: Age:

Weight: Sex: Abnormalities:

Time.	Drug.	Dose per Kg.	Strength of Solution.	Manner of Injection.	Blood Pressure			Trac. No.,
					Mean Height.	Pulse Pressure.	Respir. Variations.	
(I)					(II)			

Heart Rate, Regularity, and Strength.	Urine Flow.	Oncometer Readings.	Respiration Rate, Strength.	Remarks.
(II)	(III)	(II)	(III)	

Conclusions from individual experiments. Conclusions from class-work.

The main stress should be laid on the urine flow. The oncometer observations are optional.

Preliminary Operations.—Arrange for blood pressure tracing. Weigh and anesthetize the animal. Insert cannulæ into the tracheal and central end of carotid, and femoral vein. Connect for blood pressure and injection. Expose the kidneys (page 810). Tie cannulæ into ureters, and place them so that they will not be kinked. If oncometer readings are to be made, reach one of the kidneys by a lateral incision (page 810) and connect. Sew up the wounds. Count the rate of drops from each ureter, and take normal tracing.

Experiments.— 1. Saline Diuresis.— *Urine-flow,* Blood pressure (Chapters XXIV and XXV).— Inject intravenously 25 c.c. per Kg. of warm sodium sulphate (2.5% of dried or 5% of crystals). Collect the urine after a few minutes: The urine flow is promptly increased, and remains high for a considerable time (dilution of blood, lessened viscidity, increased quantity of blood in vessels, "hydremic plethora"). Note that the carotid pressure is not increased sufficiently to account for the diuresis. The circulatory and respiratory effects are identical with Exercise 62, No. 1. The volume of the kidney increases.

Some animals do not show any diuresis, especially if the kidneys have been injured. Should this be the case, the ureter observations may be abandoned, and replaced by myocardiogram, oncometer, or respiratory tracings.

Test the urine for chlorids ($HNO_3 + AgNO_3$), comparing it with the original bladder-urine. The chlorid has almost disappeared (due to dilution of the plasma; the chlorid could be made to reappear by the injection of sodium nitrate, iodid, bromid, or sulfocyanid. These act probably by liberating the "combined" chlorid of the plasma).

The hypodermic or intravenous injection of normal saline solution or the drinking of water increase the diuresis in the same manner as the sulphate solution. The latter would not be diuretic by mouth, as it is but imperfectly absorbed.

Diuretic factors.— In exact experiments, the urine flow is referred to the weight of the animal. v. Schroeder selects the surplus excretion per 100 Gm. of animal, calculated usually for one hour. Sollmann's factor relates to the maximal rate of secretion, being the maximum number of cubic centimeters of urine secreted in 40 consecutive minutes, per kilo of animal.

2. Theobromin.— *Ureter-flow,* Blood pressure.— When the diuresis begins to decline inject hypodermically 50 mg. per Kg. of Theobromin salt[1] (1 c.c. per Kg. of 5% solution). The urine flow increases (stimulation of renal epithelium). Note that the changes in the carotid pressure do not suffice to explain the diuresis.

The effects on the circulation are identical with those of caffein (Exercise 63, No. 4). The volume of the kidney increases.

3. Hemorrhage.— *Ureter-flow,* Blood pressure (Fig. 51, page 180; Chapter VIII).— Withdraw about 25 c.c. per Kg. of blood from the femoral artery, whilst taking a tracing. (The blood is to be whipped vigorously with a glass-rod for about 10 minutes, or until thoroughly defibrinated, strained through muslin, and heated to 40° C.)

The ureter-flow stops as the pressure falls. The heart beats are quickened and weakened. The respiration is dyspneic.

The cardiac and respiratory effects are due to anemic depression of the vagus and respiratory centers. The anuria is explained by the low blood pressure.

Observe the pressure for some five minutes after the completion of the hemorrhage: there is a slight, but very imperfect, recovery.

4. Injection of Normal Saline Solution.— *Urine-flow,* Blood pressure.— Inject 25 c.c. per Kg. of warm normal saline solution. The urine flow and the blood pressure recover considerably, but do not usually reach the original level. The effect lasts for several hours.

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[1] Diuretin or Agurin. Theocin may also be used.

Note the much larger effect as compared with saline injection in the normal animal, No. 1.

5. Injection of Defibrinated Blood.— *Urine-flow,* Blood pressure. After 15 minutes, inject the warmed defibrinated blood: The ureter-flow and blood pressure recover completely.

6. Barium Chlorid.— *Urine-flow,* Blood pressure (Chapter XXV). Expose the intestines. Inject intravenously 20 mg. per Kg. of barium chlorid (2 c.c. per Kg. of 1%) and repeat every 10 minutes until death: The effects on the heart resemble those of digitalis (Exercise 62, No. 3), but the vasoconstriction is much more prominent, and the pressure rises very high. The urine, however, is decreased, the renal arteries being also constricted. The intestines show violent peristalsis. This, and the vasoconstriction, are due to direct stimulation of the unstriped muscle.

7. Chloroform Rigor.— (Chapter XIX).— Inject some chloroform into the peripheral end of one femoral artery: this causes immediate rigor of this leg.

Excise the suprarenal capsules and place in 10 c.c. of 50% glycerin.

Summarize the effects of Sulphates and of Hemorrhage in Chapter XXXVIII, Nos. 23 and 24.

EXERCISE 66.—EFFECTS OF DRUGS ON PERISTALSIS (INTRODUCTORY).

Drugs which increase peristalsis may be grouped as *cathartics;* those which diminish peristalsis as *antidiarrhœica.*

Whilst peristalsis, and especially defecation, are to some degree controlled by the central nervous system, almost all the drugs which influence them act peripherally. The remedies which are utilized therapeutically to influence peristalsis are mainly direct irritants, chemic or mechanic (consult Exercises 31 and 46, No. 5, and 63, No. 1), or astringents. These act only when they are introduced into the alimentary canal.

Peristalsis may also be influenced by **peripherally-acting muscle-nerve poisons.** They are rarely used in therapeutics, because their effects are not confined to the intestinal tract; but they are of considerable importance in toxicology and pharmacology. This group comprises the same drugs which have been studied in connection with the vagus (Exercise 50), pupil (Exercise 54), and salivary glands (Exercise 55); and the effects are essentially similar.

The peristaltic movements are arrested by atropin, stimulated by muscarin, physostigmin, pilocarpin, and nicotin. There is a mutual antagonism between atropin on the one hand, and muscarin, pilocarpin and physostigmin on the other: The effect corresponding to whichever drug is present in excess. Atropin prevents the effects of nicotin, but not vice versa. Barium is active after atropin, but not the reverse.

By transferring the conclusions drawn from the iris and salivary gland to the intestine, it is generally assumed that:

Atropin paralyzes the endings;

Muscarin, pilocarpin, and physostigmin stimulate the endings; pilocarpin also the ganglia; physostigmin also the muscle.

Nicotin stimulates the ganglia, paralyzing them in large doses.

Barium stimulates the muscle.

This may serve as a simple working hypothesis; but the facts are in reality much more complicated, and cannot be satisfactorily explained until the physiology of peristalsis is better understood.

Innervation of the Intestine.— The subject has been worked out mainly on the small intestine of dogs and cats, and it is not impossible that the details are somewhat different in other animals.

Central Innervation.— This consist in:

(*a*) tonic inhibitory impulses passing down the splanchnic to the local centers,

(*b*) both inhibitory and augmentor fibers contained in the vagus; the latter are not tonically active, and are very easily eliminated by other influences.

Outside Influences.— The peristalsis is very greatly affected through changes in the circulation which are not very easy to control and to interpret. When the abdomen is opened, as is necessary for an analysis of the phenomena, the exposure to the air, or to the salt solutions, which are probably not quite indifferent; the abnormal conditions of pressure; the inattention to exact regulation in temperature; the setting-up of direct or reflex stimulation or inhibition by the unavoidable handling of these organs or by the attachment of apparatus; the relative difference in longitudinal and circular coats in different animals; the nervous supply, which is perhaps quite different in different species; the variable activity of the central nervous system;— all these are complicating factors which seem to influence the results in an extremely strong manner, and which it is absolutely impossible to exclude.

Peripheral Innervation.— This seems to be the more important, and can be studied under uniform conditions, according to Magnus' method (page 888).

The intestine exhibits several varieties of apparently independent movements, of which the rhythmic pendulum movements and the peristaltic reflex appear to be the most important. These can also be seen in the excised intestine. The pendulum movements are automatic; the peristaltic movements, on the other hand, are reflex. This peristaltic (Bayliss-Starling) reflex may be elicited by pinching the intestine especially if the restraining influence of the splanchnics is eliminated. It consists of two phases: a constriction above the point of stimulation, and a dilation below this point. This is especially useful in the propulsion of the intestinal contents, the reflex descending along the intestine, which is thereby stripped. The pendulum movement is probably concerned in absorption, dividing the intestinal contents so as to give a larger surface.

The local nerve-muscle mechanism for these reflexes consists of the longitudinal and circular muscular coats, innervated by Auerbach's plexus of nerve cells and fibers, which lies between them. This communicates also with Meissner's plexus in the submucosa, which innervates the glands, muscularis mucosæ, etc., but which is not concerned in the intestinal movements.

Magnus has succeeded in making preparations from the intestine, consisting of muscle and nerve endings, with or without the plexus. By means of these he has demonstrated that the rhythmic movements and the Bayliss-Starling reflex require the presence of Auerbach's plexus. When this is removed, the muscle responds to stimulation by a simple contraction, or by tetanus.

The investigation of drugs on these preparations lead him to the following conclusions as to the most peripheral action:

Atropin in small doses stimulates Auerbach's plexus, but prevents the stimulation of muscarin, pilocarpin, and physostigmin, and the inhibition of nicotin; it has little effect on the stimulation by strophanthin or barium. In medium doses, it renders the rhythmic movements more regular. In larger doses, it paralyzes the muscle.

Apocodein also stimulates Auerbach's plexus in small doses, and paralyzes the muscle in larger doses.

Nicotin at first inhibits the movements, by an action peripheral to the plexus; it then stimulates the plexus.

Suprarenin inhibits the movements, acting on the nerves peripheral to the plexus.

Muscarin stimulates the plexus.

Pilocarpin, Physostigmin, and Strophanthin stimulate the nerves peripheral to the plexus, large doses of strophanthin paralyze these structures.

Barium stimulates the muscle.

EXERCISE 67.—EXPERIMENTS ON PERISTALSIS (AND BLOOD PRESSURE).

Read Exercise 66.

Special Materials Needed:

Small dog, not morphinized; or rabbit, anesthetized by 3 c. c. per Kg. of 20% chloral administered by stomach. (The dog permits better blood pressure tracings, but rabbits show the peristaltic phenomena at least equally well; a narrow-caliber manometer must be used for rabbits.)

Sodium chlorid (small crystal); Physostigmin, $^1/_{10}$% (1 c. c.); Barium chlorid, 1% (1 c. c.); Atropin, $^1/_{10}$% (1 c. c.); 1% (10 c. c.); Pilocarpin, $^1/_{10}$% (30 c. c.); Nicotin, 1% (5 c. c.); Arsenate of sodium, 1% (50 c. c.).

Distribution of Work (see page 790):

Students A and B = place I; C and D = II and electric stimulation; E and F = III (observation of peristalsis and respiration).

Observations Required:

Date: Animal: Age:

Weight: Sex: Abnormalities:

TIME.	DRUG.	DOSE per Kg.	STRENGTH OF SOLUTION.	Manner of Injection.	BLOOD PRESSURE Mean Height.	BLOOD PRESSURE Pulse Pressure.	BLOOD PRESSURE Respir. Variations.	Trac. No.
(I)					(II)			

HEART Rate, Regularity, and Strength.	INTESTINE Color Peristalsis.	RESPIRATION Rate, Strength.	REMARKS.
(II)	(III)		

Conclusions from individual experiments;
Conclusions from class-work:
The main stress should be laid on the peristalsis.

Preliminary Operations.— Arrange for blood pressure tracing. Weigh and anesthetize the animal. Insert cannulæ in trachea, central end of carotid, and femoral vein.

Experiments.— A. Local Application.— Make a small incision in the linea alba and draw forth a loop of small intestine.

1. **Bayliss-Starling Reflex.**— Observe that pinching with forceps causes a spreading peristalsis (*mechanical stimulation*); the intestine contracting above the stimulus, and relaxing below.

2. Apply a crystal of *salt:* spreading peristalsis (salt-stimulation).

3. Apply at another place a few drops of $^1/_{10}$% *physostigmin:* local constriction (stimulation of muscles and endings).

4. Apply at another place a drop of 1% *$BaCl_2$:* strong constriction (stimulation of muscle).

5. Apply at another place a drop of $^1/_{10}$% *atropin:* Peristalsis ceases. See whether 3 to 6 are effective. (Physostigmin is effective, barium and salt ineffective; pinching produces a slight effect.)

B. Systemic Administration.— Connect for blood pressure and injection. Open the entire abdomen along the linea alba, so that the intestines may be observed. Take normal tracing and observations.

The odd sets proceed with No. 6, the event sets with No. 7. All sets do No. 8 to end.

6. **Pilocarpin.**— (Fig. 57, page 252; Chapter XII.) — Inject intravenously 3 mg. per Kg. of Pilocarpin (3 c. c. per Kg. of $^1/_{10}$%): The peristalsis is increased (stimulation of the ganglia and muscle). Salivation may be noticed (stimulation of salivary ganglia and endings). The heart is at first slowed, but may be quickened later (peripheral stimulation and depression of vagus).

7. **Nicotin.**[1]— (Fig. 59, page 260; Chapter XII).— Expose the vagus and find the smallest stimulus which just stops the heart. Inject subcutaneously 5 mg. per Kg. of nicotin (½ c. c. per Kg. of 1%). The peristalsis is greatly increased. The effects on the circulation are shown in Fig. 60. The respiration is also increased and the animal may become convulsive. When the heart has become quickened, note that stimulation of the vagus does not stop the heart (depression of the vagus ganglion cells). Very strong stimulation may cause some slowing, if the paralysis is incomplete.

8. **Atropin.**— (Fig. 55, page 230; Chapter XI).— (*a*) Expose the vagus and determine the smallest stimulus which will just stop the heart. Inject intravenously 10 mg. per Kg. of Atropin (1 c. c. per Kg. of 1%): the peristalsis and salivation cease (paralysis of endings). The heart is quickened, and stimulation of the vagus becomes ineffective (paralysis of vagus endings). The blood pressure is not much altered; there may be a slight rise. (The rate of the heart will not be changed by the atropin, if the pilocarpin or nicotin paralysis was complete.)

9. **Arsenic.**— (Chapter XXVII).— Inject intravenously 5.0 mg. per Kg. of Arsenate of sodium (5 c. c. per Kg. of 1%): the intestines show capillary congestion and become filled with fluid (paralysis of the capillary walls). The blood pressure falls, but rises at once if the aorta is temporarily compressed, showing that the cardiac muscle is not injured (except by larger doses). Observe half an hour if necessary. Kill the animal, excise the suprarenals, cut them up, and place them in 10 c. c. of 50% glycerin.

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[1] *Nicotin on ganglia and nerve fibres* (Optional). Expose the superior cervical ganglion of an anesthetized rabbibt. Stimulation causes constriction of the ear vessels and dilation of the pupil. Paint 1% nicotin on the nerve below the ganglion. A stimulus applied central to this point is still effective, showing that the nerve fibers are not paralyzed by the poison. Paint the nicotin on the ganglion. Stimulation of the nerve is now ineffective, showing paralysis of the ganglion.

Summarize the effects of Physostigmin, Pilocarpin, Nicotin, Atropin, and Arsenic in Chapter XXXVIII, Nos. 27 to 31.

EXERCISE 68.—PERFUSION OF EXCISED ORGANS (INTRODUCTORY).

(Review Exercises 51 and 57.)

The perfusion of excised organs permits the study of their functions under simple conditions, which can be modified at pleasure. If the purpose of the study concerns the proper vital functions of the organ, the conditions must be made to approach those of the body as closely as possible: The perfusing fluid must be at the proper temperature (38° C.) and pressure (about 130 c.m. of water); the perfusion fluid must consist of well-oxygenated Locke's Fluid (see Index), if possible with the addition of the defibrinated blood of the same animal. In delicate experiments it is necessary to imitate the rhythmic pulse-pressure.

If the study concerns merely the circulation, plain saline solution may be used at room temperature: the blood vessels maintain their vitality for many hours, even under these unfavorable conditions. The simplest disposition which will suffice for the experiment should be preferred, as the advantages of more complicated apparatus are often offset by the chances of accident, etc. The arrangement described on page 819 answers for the circulation; that of Fig. 127 is used when the perfusion is to be made at body temperature. The perfusing fluid must be free from dirt. The outflowing fluid is collected, strained, and returned to the reservoir. Fluid mixed with poisons is kept separate. The administration of drugs may be done with a hypodermic syringe, thrusting the needle obliquely through the rubber, just before it connects with the arterial cannula. The injection must be made so slowly that the pressure is not materially raised. More exact results are obtainable by employing two reservoirs, joined to the arterial cannula by a T piece. If the injection is to be made at body temperature, a thermometer is introduced in a T piece, as in Fig. 127. The greatest care must be used to exclude air from the apparatus. If any should enter, it can be removed through the side piece of the T. The perfusion of each drug is continued only until the desired effect is obtained.

The preparation of the organs is described on page 810. The effect on the vessels may be judged from the rate of outflow, and from the volume of the organ, by taking oncometer readings. The flow through the intestine and spleen is too rapid for counting, if saline solution is perfused; it is therefore advisable to lower the reservoir until it is just possible to count the drops. The changes of the flow and oncometer should be plotted as curves, each ordinate representing five minutes, each abscissa ten drops of flow, or ½ c.m. of the oncometer. The excised kidney is particularly well adapted to the study of a great variety of problems (Sollmann and Hatcher, American Journal of Physiology, 1905, XIII, p. 241–303).

The heart methods are simplified modifications of those proposed by the originators.

Preparation for Exercises 69 to 73.—These exercises may be performed in one day, being distributed amongst the sets. (Exercises 74 to 76 may also be done in one day, by assigning them to different sets.)

Special Materials Needed (Exclusive of Solutions):

For two sets: Morphinized dog, porcelain dish, glass rod, large funnel, cotton, beaker.

For each half set:

Exercise 69: Simple perfusion apparatus, arranged for raising and lowering; renal artery, vein and ureter cannulæ, with outflow tips; meter rubber tube; tall stand and clamp; oncometer, bench, and clamps to hold organ and cannulæ; 2 tumblers; 250 c. c. graduate.

Exercise 70: Simple perfusion apparatus with T piece, at 140 c. m. Other apparatus as in 69, omitting meter-tube and tall stand.

Exercise 71: As in 70.

Exercise 72: As in 70; it is advisable to have a second, smaller reservoir in this exercise; spectroscope.

Exercise 73: As in 70, omitting the ureter cannula.

Solutions Needed:

Exercise 69: 2% NaCl (2 L.).

Exercise 70: 1% NaCl (2 L.); Distilled water (1 L.); 5% NaCl (2 L.); $CaCl_2$, 16.33 Gm. of salt dried at 110° C., added to 1 L. distilled water;[1] Sodium citrate, 27.37 Gm. of salt dried at 110° C., added to 1 L. distilled water.[1]

Exercise 71: 1% NaCl (2 L.); Adrenalin, 1 : 1,000 (2 c. c.); HCN, 2% (5 c. c.); Digitalis, 10% (5 c. c.); Chloral, 10% (5 c. c.); Barium chlorid, 1% (10 c. c.).

Exercise 72: 1% NaCl (1 L.); Diluted Blood (2 L.); Caffein Sod. Benzoate, 1% (10 c. c.); HCN, 2% (5 c. c.); Digitalis, 10% (5 c. c.); Ammonium sulphid.

Exercise 73: 1% NaCl (2 L.); 10 c. c. each of Adrenalin, 1 : 10,000; Sodium nitrite, 1%; Digitalis, 1%; Chloral, 1%; Barium chlorid, $^1/_{10}$%.

Preliminary Operations (For two full sets).

1. Anesthetize a large dog; place cannulæ into trachea, and central end of one carotid artery and femoral vein. Draw as much blood from the carotid as will flow readily. Defibrinate this. Inject into the vein 75 c. c. per Kg. of NaCl (1%). Again draw blood and defibrinate. Mix the blood and filter through a funnel plugged loosely with absorbent cotton.

Meanwhile open the abdomen of the dog by a long median incision. Expose one of the kidneys freely by cutting along the lower border of the rib. Clean the fat and nerves away from the organ and especially from the vessels and ureter.

Tie cannulæ into ureter and renal artery (should this be double, ligate the smaller branch). Connect with perfusion apparatus, previously filled with the solution (2% NaCl for Exercise 69; 1% NaCl for the others). Flush the kidney, until the vein is almost colorless. Stop the perfusion. Insert cannula into renal vein and adjust outflow-tip. (All the cannulæ point toward the kidney). Excise the kidney. Adjust it in the oncometer, on the bench. Immobilize the cannulæ by clamps or some other means, and see that they are not kinked or twisted. Start the perfusion. Observe that the oncometer rises. Proceed with Exercise 69 or 70.

2. As soon as the first kidney is excised, prepare the other in the same manner, and proceed with Exercise 71 or 72.

3. Expose the spleen. Insert cannula into the largest artery. Flush. Insert vein cannula. Tie all other branches. Excise and adjust like the kidney, and proceed with Exercise 73.

4. Expose a large mesenteric artery and vein; insert cannulæ as in 3. Excise the intestine, and proceed with Exercise 73.

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[1] These solutions should have the same freezing point as 1% NaCl.

EXERCISE 69.—EFFECT OF CIRCULATION ON THE KIDNEY.

1. **Effect of Arterial Pressure.**—Observe the vein and ureter-flow (drops or c. c. per minute), with the reservoir at 140 c.m. above the kidney (after the solution has run for about 10 minutes). Lower the reservoir to 100 c.m., and repeat the observations after 10 minutes; also with 60 and 20 c.m.

The vein flow, ureter flow, and oncometer (also the maximal vein and ureter pressure) vary in the same direction as the arterial pressure.

(By modifying the arrangement so that the pressure can be interrupted rhythmically, it can also be shown that the vein and ureter flow are much better with interrupted pressure than with constant pressure of the same mean height,)

2. **Effect of Vein Pressure.**—Replace the reservoir at 140 c.m. Remove the outflow-tip from the vein cannula, and connect this with a rubber tube, 1 m. long. Replace the outflow-tip in this tube and support it at the level of the kidney. Let it fill with the fluid, and in 10 minutes measure the vein and ureter flow and the oncometer. Raise the vein outflow to 30 c.m. above the kidney and in 10 minutes repeat the observation; also at 60 and 90 c.m. Increase of vein pressure increases the oncometer, but diminishes the vein and ureter flow. The diminution is gradual up to 60 or 80 c.m., when there is a sharp drop. The diminution is due to the pressure of the distended veins on the urinary tubules and on the arterial end of the circulation.

3. **Effect of Ureter Pressure.**—Remove the tube from the vein and connect it with the ureter cannula. Repeat the observations as in 2. The effects are similar, but the ureter pressure has a comparatively small effect on the vein flow and oncometer.

4. **Occlusion of the Vein.**—Disconnect the tube. Count the ureter-flow and observe the oncometer. Pinch the vein tube to complete occlusion. The oncometer increases. There is a short spurt of ureter fluid, and then almost (but not quite) complete anuria (compression of the urinary tubules in the boundary layer).

5. **Injection by Renal Vein.**—Release the vein and after 10 minutes count the vein and ureter flow and observe the oncometer. Change the injection tube from the artery to the renal vein: Almost no fluid will run from the artery or ureter, the oncometer increasing greatly. (A valvular mechanism exists in the kidney, probably by the pressure of the distended veins on the arterial capillaries in the glomeruli.)

Summarize in Chapter VI, No. 35.

EXERCISE 70.—SALT AND ION ACTION ON THE KIDNEY.

Perfuse the kidney with 1% *NaCl* solution, and observe the vein and ureter flow (drops per minute) and the oncometer after 10 minutes.

1. **Hypoisotonic Solutions.**—Replace the salt solution by water (removing the solution through the T piece, avoiding air bubbles). The vein and ureter flow and the volume are diminished. This is due to the swelling of the renal cells, obstructing the access of the fluid to the kidney.

2. **Hyperisotonic Solutions.**—Replace by 5% NaCl. The flow increases much above the original, the volume to about the original (lessened resistance by shrinkage of cells).

Return to 1% NaCl solution. After 15 minutes replace this by:

3. **Calcium Chlorid** (Isotonic with 1% NaCl).—The flow and

oncometer are diminished. This is a specific (ion) effect of the calcium.

4. **Citrate.**— Replace by isotonic sodium citrate: The flow and oncometer are increased. The citrate acts as a hyperisotonic solution, since it does not penetrate the cells as readily as NaCl (consult Exercise 23, No. 3).

5. **Occlusion of Vein.**— Pinch the tube of the vein-cannula to complete occlusions. See Exercise 69, No. 4.

Summarize the effects of Osmosis, of Calcium, and of Citrate in Chapter XXXVIII, Nos. 32 to 34.

EXERCISE 71.— EFFECTS OF DRUGS ON EXCISED KIDNEY.

Perfuse with 1% NaCl. After 15 minutes observe the vein and ureter flow (drops per minute) and the oncometer.

1. **Adrenalin.**— Change (see Exercise 70, No. 2) to 1 : 50,000 (1 c.c. of 1 : 1,000 to 50 c.c. of 1% NaCl). The flow and volume are diminished (constriction of arterioles).

2. **Hydrocyanic Acid.**— Change to 1 : 2,500 HCN (2 c.c. of 2% to 100 c.c. of 1% NaCl): increase of vein, ureter and oncometer (dilation of arterioles). This effect of hydrocyanic acid seems to be confined to the kidney.

3. **Digitalis.**— Change to 1 : 1,000 Digitalis (1 c.c. of 10% to 100 c.c. of 1% NaCl): vasoconstriction.

4. **Chloral.**— Change to 1 : 1,000 chloral (1 c.c. of 10% to 100 c.c. of 1% NaCl): vasodilatation.

5. **Barium.**— Change to 1 : 2,000 barium chlorid (5 c.c. of 1% to 100 c.c. of 1% NaCl): vasoconstriction.

EXERCISE 72.— BLOOD AND DRUGS ON EXCISED KIDNEY.

1. Perfuse with 1% NaCl. After 15 minutes observe the vein and ureter flow (drops per minute) and oncometer. Change to (see Exercise 70, No. 2):

2. **Blood,** diluted with about three volumes of 1% NaCl. The vein flow is promptly increased, whilst the ureter flow and oncometer are greatly diminished. Note the darkening of the venous blood. The flow is again somewhat slowed after a time.

Two factors are concerned in these effects: The great viscidity of the blood, which would slow the flow and diminish the volume. In dead kidneys the vein flow is practically arrested. In living kidneys, however, the blood stimulates a vasodilator mechanism, probably in the efferent arterioles, which causes the vein flow to continue, and generally increases it above normal.

3. **Saline Diuretics.**— After about 15 minutes repeat the observations. (The vein flow will be somewhat slowed, on account of the increasing viscidity.) Add about 30% of 1% NaCl to the perfusing blood: The flow and volume are increased (lessened viscidity, and consequently lesser resistance). Use this blood dilution in all subsequent experiments.

4. **Caffein.**— Substitute diluted blood with 1 : 5,000 caffein-sodium benzoate (4 c.c. of 1% to 100 c.c. of diluted blood): Somewhat increased flow and volume. (Not always successful.)

5. **Hydrocyanic Acid.**— Substitute blood with 1 : 2,500 HCN (2 c.c. of 2% to 100 c.c. of diluted blood): Further vasodilation.

Note that the venous blood is not darkened, but that it is readily reduced by ammonium sulphid. (Cyanids prevent the reduction of blood by paralyzing the oxygen-consuming metabolism of the cells.)

6. Digitalis.— Substitute blood with 1:1,000 Digitalis (1 c.c. of 10% to 100 c.c. of diluted blood): Strong vasoconstriction.

Summarize the effects of Cyanids and of Normal Saline Solution in Chapter XXXVIII, Nos. 36 and 37.

EXERCISE 73.— CIRCULATION THROUGH EXCISED SPLEEN OR INTESTINE.

In this exercise, the drugs are injected slowly into the circulation by means of a hypodermic syringe. The experiment may be modified by adding the drugs directly to the perfusing fluid, and by using cold or warm defibrinated blood.

1. Perfuse with 1% *NaCl* and in 10 minutes observe the rate of flow (drops per minute) and oncometer.

2. Suprarenal.—Inject 5 c.c. of 1:10,000 adrenalin: vasoconstriction.

3. Nitrites.— Inject 5 c.c. of 1:100 sodium nitrite: vasodilation.

4. Digitalis.— Inject 5 c.c. of 1:100 digitalis: vasoconstriction.

5. Chloral.— Inject 5 c.c. of 1:100 chloral: vasodilation.

6. Barium.— Inject 5 c.c. of 1. 1,000 barium chlorid: vasoconstriction.

Instead of injecting the stronger solutions, weaker concentrations may be perfused as in Experiment 71:

2. Adrenalin, 1:50,000 = 2 c.c. of 0.1% to 100 c.c. of 1% NaCl.
3. Sodium Nitrite, 1:2,000 = ½ c.c. of 10% to 100 c.c. of 1% NaCl.
4. Digitalis, 1:1,000 = 1 c.c. of 10% to 100 c.c. of 1% NaCl
5. Chloral, 1:1,000 = 1 c.c. of 10% to 100 c.c. of 1% NaCl.
6. Barium, 1:20,000 = ½ c.c. of 1% to 100 c.c. of 1% NaCl.

Summarize the effects of Nitrites and Barium in Chapter VI, Nos. 38 and 39.

EXERCISE 74.— EXCISED MAMMALIAN HEART (LANGENDORFF).[1]

Review pages 895 to 898.

Special Materials Needed:

Morphinized dog.

Perfusion apparatus (Fig. 127, see below); Bone Forceps; Aortic Cannula; Large evaporating dish, glass rods, large funnel and cotton, 2 large beakers, oxygen-tank.

7 Liters of Locke's Fluid (see Index) at 40° C.; 15 c.c. each of Strychnin, 1:5,000; Caffein, 1:5,000; Chloroform, saturated in normal saline; Adrenalin, 1:10,000; Potassium chlorid, 1:100; Camphor, saturated in normal saline; Digitalis, 1:100.

Distribution of Work (see page 790):

Students E and F = place I; A and B = apparatus and tracings; C and D = place III and heart-count. If several sets do the experiment, one may attempt all the numbers, another may do 1, 2, 5, 6, and 7, a third 1, 2, and 7.

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[1] Exercises 74 to 76 are assigned to different sets.

Observations Required:

TIME.	DRUG.	STRENGTH OF SOLUTION.	Injected. Quantity	HEART Rate, Regularity, and Strength.	Tracing Number.
(I)				(III)	(II)

REMARKS.
(III)

Conclusions from individual experiments:

Conclusions from class-work:

Perfusion Apparatus (See Fig. 127).—A large water bath *w.b.*, heated by a Bunsen or alcohol burner, is arranged on a shelf, 150 c.m. above the table. In this is set a 2-gallon bottle, containing 7 liters of fresh Locke's Fluid. Into this bottle dips a siphon, a narrow orifice tube connected with the oxygen-tank, and a thermometer. The siphon tube is prolonged to the table. A T piece, *t'* [1] is inserted near the lower end, the free limb being closed by a Mohr's clamp. The tube terminates in another T, *t''*, which bears the bulb of a thermometer. This T is joined to the aortic cannula, and supported by a clamp and stand, over the hot-water funnel *f*. This is kept warm by a Bunsen or alcohol flame. A pin is hooked to the apex of the heart, *h*, and connected with a string, which passes through the stem of the funnel to a muscle lever, *m. l.*, writing on the drum *d*. The lever is weighted with a 10 Gm. counterpoise. It is best to attach the string to the lever with a pin, so that the excursions can be regulated to 1½ or 2 inches. A beaker is set beneath the funnel to catch the blood. Several drums should be smoked in advance. The whole apparatus should be ready before the heart is excised.

Preliminary Operations.—Whilst the apparatus is being set up, the dog is anesthetized, and cannulæ are tied in the trachea, carotid, and femoral vein. The latter is connected with the injection burette. The dog is now bled from the carotid as long as the blood flow is a strong stream. The carotid is clamped, and the blood is defibrinated, strained, and heated to 45° C. and poured into B. The heart is now exposed as described on page 809, and artificial respiration is started. The carotid is again opened, and the dog is bled, whilst at the same time a liter of warm Locke's Fluid is allowed to flow into the femoral vein. The diluted blood is collected as long as it flows from the carotid, defibrinated, strained, mixed with the blood which was previously drawn, heated to 45° C., and poured into the reservoir.

The reservoir is now shaken, so as to mix the fluids, and a slow stream of oxygen is passed through it. The siphon tube is filled with the blood.

In the meantime the heart is excised with an inch of the aorta, and with the lungs. The latter are trimmed away, the pericardium is slit open. All branches of the aorta are tied. The aortic cannula (page 807) is introduced and secured by a firm ligature, taking care that it does not interfere with the play of the semilunar valves. The aorta is clamped below the cannula; this is filled with blood, connected air-free with T′, and supported in the clamp. The pin is hooked into the apex, connected with the lever, the clamp on the aorta is removed, and the perfusion is started. The pressure closes the semilunar valves, so that the fluid is forced through the coronary circulation, escaping through the right auricle (Fig. 124, page 896) and into the beaker. The flow should be rather free, the beaker being frequently exchanged, the unpoisoned blood being returned to the reservoir. If it is too free, some of the veins may be closed by bulldog forceps. See that the thermometer in T″ registers 38 to 42° C.

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[1] This serves for the removal of air or of cooled blood, if the flow has been arrested.

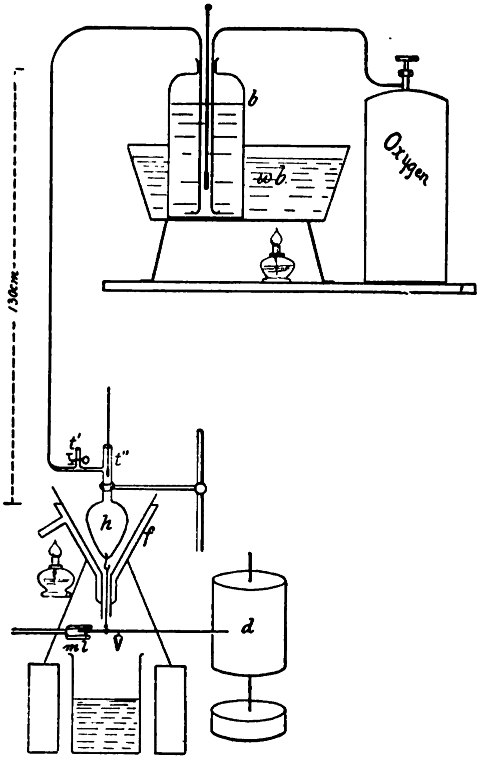

Fig. 127, Apparatus for Langendorff Heart (see text).

The heart will begin to beat in a very short time, at first feebly and irregularly, but soon with strong, regular beats. The observations and tracings may be started at this time. The solutions should be injected just below T′ with a hypodermic syringe, thrust obliquely through the rubber. The injections should be made *very slowly,* and continued until the desired effect is obtained.

(Instead of injecting the drugs with a syringe, they may be added directly to the perfusing fluid, in the proportion of about 1:25. A second reservoir will be necessary.)

Experiments.— 1. Strychnin.—(Fig. 46, page 149; Chapter VIII). —Obtain a normal tracing. Inject 1:5,000 Strychnin. According to the dose (which is really inversely proportional to the rate of perfusion), one may obtain:

(*a*) no effect;
(*b*) increased excursions (Fig. 46 E);
(*c*) diminished excursions (Fig. 46 F).

2. **Caffein.**— (Chapter VIII).— Inject 1:5,000 Caffein. According to the dose one may obtain quickening and increased excursions; or slowing with diminished excursions.

3. **Chloroform.**—(Fig. 82 F, page 430; Chapter XIX).— Inject a saturated solution of chloroform in normal saline: The heart is slowed and especially weakened. Proceed to 4 before it has quite stopped.

4. **Adrenalin.**— (Fig. 63 and 64, page 290; Chapter XIII). Inject 1:10,000 adrenalin: The heart revives promptly and beats powerfully.

5. **Potassium.**—(Fig. 91, page 557; Chapter XXV).— Inject 1:100 KCl: Sudden paralysis of the heart. Recovery may be spontaneous, or occur by 6, which should be undertaken at once.

6. **Camphor.**— (Chapter XXI).— Inject a saturated solution of camphor in normal saline solution: The heart revives or is strengthened.

7. **Digitalis.**— (Chapter XXII).— Inject 1:100: The heart is first quickened and strengthened. The tonus increases. Finally it goes into delirium cordis and stops in systolic position. Compare the effects with those in an intact animal, Exercise 62, No. 3.

Summarize the effects of Suprarenal, Potassium, and Camphor in Chapter XXXVIII, No. 40 to 42.

EXERCISE 75.—ISOLATED MAMMALIAN HEART (MARTIN AND APPLEGARTH).

Review pages 000 and consult Fig 124, page 000.

Special Materials Needed:

Morphinized dog.
Liter injection-bulb, suspended 1.4 meters above the table, connected with a tube reaching to the table, terminating in an aortic cannula, and closed by a Mohr's clamp. Muscle-lever and drum. Capsule, glass rod, funnel, cotton, and beaker (for defibrinating blood). Bone-forceps.
0.9% NaCl solution at 45° C. (½ L.); Digitalis, 1% (10 c.c.).

Distribution of Work (see page 790):

Students A and B = place I; C and D = apparatus and tracings; E and F = III and heart count.

Obervations Required:

TIME.	DRUG.	STRENGTH OF SOLUTION.	Quantity Injected.	HEART Rate, Regularity, and Strength.	Tracing Number.
(I)				(III)	(II)

REMARKS.
(III)

Conclusions from individual experiments:

Conclusions from class-work:

Preliminary Operations.— Anesthetize. Place cannulæ into trachea and carotid. Draw 150 c. c. blood; defibrinate; strain through cotton. Mix with 500 c. c. of warm saline. Fill injection funnel and tube, free from air. Commence artificial respiration; open chest. Slit pericardium. Isolate aorta and vena cava. Insert aortic cannula central to origin of carotid. Remove clamp on injection tube. Tie vena cava at entrance into heart. Hook pin into the apex, and connect with muscle-lever. Take normal tracing and observations.

Inject 1% **Digitalis** very slowly into the aortic cannula, with a hypodermic syringe. Consult Exercise 74, No. 7.

EXERCISE 76.—ISOLATED MAMMALIAN HEART (BOCK'S METHOD).

Review pages 000.

Special Materials Needed:

Morphinized dog. Y piece. Screw clamp.

10 c. c. each of Strychnin, $^1/_{100}$%; Caffein, $^1/_{100}$%; Chloroform, saturated in normal saline; Digitalis, $^1/_5$%.

Distribution of Work (see page 000):

Students C and D = place I; E and F = II; A and B = III.

Observations Required:

Date:

Weight of animal:

				Blood Pressure			
Time.	Drug.	Strength of Solution.	Quantity Injected.	Mean Height.	Pulse-Pressure.	Respir. Variations.	Trac. No.
(I)				(II)			

Heart Rate, Regularity, and Strength.	Remarks.
(III)	

Conclusions from individual experiments:

Conclusions from class-work:

Preliminary Operations.— Prepare for blood pressure tracing.

Anesthetize the dog. Tie cannulæ into the trachea, into both carotids and in one external jugular vein (page 809). Connect one carotid for blood pressure. Join the other carotid and the jugular by the Y piece, connecting the third limb of the Y with the injection burette (Fig. 124, page 896). (The pressure apparatus is superfluous; sufficient force can be exerted by blowing into the burette.) Place a screw clamp on the carotid, central to the Y, and a pinch-cock on the burette. Fill the connections with saline. Begin artificial respiration. Open the chest; place ligatures around the aorta (just below the carotids) and on the inferior vena cava. Tighten the ligatures simultaneously and open the clamps on the neck vessels. Adjust the screw clamp on the artery so that the circulation is free, but the blood pressure fairly high. Take tracing and observations.

Experiments.— 1. Strychnin, 1 : 10,000: See Exercise 74, No. 1. If the subclavian artery has not been tied, the animal may exhibit Baglioni's phenomenon: On striking the foreleg, the whole animal goes into convulsions; if the hindlegs are struck, there is no convulsion.

Explanatory.—The conditions are shown in Fig. 45, page 145, (the experiment being usually performed on a frog). The lower portions of the cord have been practically excluded from the circulation by the ligation of the aorta. Only the upper portion is therefore exposed to the strychnin. The path ———— goes through a poisoned sensory to an unpoisoned motor cell. Its excitation causes convulsions. The path — — — — goes through an unpoisoned sensory and a poisoned motor cell. Its stimulation does not produce convulsions. It must be concluded that the convulsant action of strychnin is exerted on the sensory and not on the motor cells of the cord.

2. Caffein, 1 : 10,000: See Exercise 74, No. 2.

3. Chloroform, saturated solution in normal saline: See Exercise 74, No. 3.

4. Digitalis, 1 : 500: See Exercise 74, No. 7.

Summarize the effects of Strychnin, Caffein, Anesthetics, and Digitalis in Chapter XXXVIII, No. 43 to 46.

CHAPTER XXXVIII.

SUMMARIES OF THE ACTIONS OF DRUGS.

The student will enter the condensed conclusions of the experiments in these schedules. The summaries in the text-book may serve as models, and the explanatory text may be consulted; but the student should accustom himself to draw critical independent conclusions. These should be committed to memory.

This chapter will also serve as an index guide to the experiments. The numbers refer to the exercises. The drugs are arranged in the order in which their study is completed in the practical work.

No. 1. Cannabis Indica (24. II).
Symptoms:
Absorption:

No. 2. Effects of Colloids, etc., on Absorption and Irritation (18 C—24. IV—25):

No. 3. Excretion of iodid (13.8—26.1—27.1 and 2).
Urine:
Saliva:

No. 4. Permanganate in Poisoning (14—29 II).

No. 5. Apomorphin (28.3—30.1).
Emetic Action:
Effects on Pulse and Respiration:
Effects on higher centers:
Idiosyncrasy:

No. 6. Zinc and Copper Sulphate (30.2).
Emetic Action:

No. 7. Colchicum (32.1).
General Symptoms:
Alimentary Canal:

No. 8. Mercury.
Alimentary Canal (32.2):
Kidneys (33.5):
Eye (27.2):
Infusoria (20.3):

No. 9. Phorrhizin (34.1).
Urine:

No. 10. Antipyrin.
Temperature (36.6 and 7):
Hemoglobin (21):

No. 11. Picrotoxin (38. II).
Motor System:
Symptoms:

No. 12. Sapotoxin.
Muscle and Nerve (42. IV):
Mucous Membranes (18. B):
Blood (22):

No. 13. Quinin.
Muscle (45):
Heart (49):
Leucocytes (20.5):
Infusoria (20.3):
Yeast (20.2):

No. 14. Cocain.
Sensation (43.III) — also Eucain and Yohimbin; Orthoform (27.3):
Taste (43. II):
Motor Nerve (43. IV):
Pupil (27.3 — 54.4):
Vessels (27.3):
General Symptoms (36.3):
Temperature (36.3):
Infusoria (20.3):

No. 14a. Dionin (54.4).
Conjunctiva:

No. 15. Asphyxia and Carbon Monoxid.
General Symptoms (39. IV):
Motor Effects (39. IV):
Circulation and Respiration (58.8):
Hemoglobin (21):
Treatment (39. IV — 58.9):

No. 16. Ergot.
Circulation and Respiration (59.3):
Rooster's Comb (51.1):

No. 17. Carbolic Acid.
Local Actions (18. C):
Circulation and Respiration (59.5):
Motor System (59.5):
Treatment (18. C — 59.6):
Hemoglobin (21):

No. 17a. Hydrastis (59.3a).
Circulation:

No. 17b. Hydrastinin (59.3b).
Circulation:

No. 18. Ammonia Inhalation.
Respiration (58.6 — 61.2):
Vagus (28.1 — 52.1):

No. 19. Morphin.
General Symptoms Central Nervous System —
  Frogs (41. I):
  Mammals (36.2 — 40. I):
  Idiosyncrasy (40. I):
  Respiration (36.2 — 61.5):
  Heroin on Respiration (61.4):
  Gastrointestinal Canal (30.4):
  Temperature (36.2):
  Glycosuria (34.2):

No. 20. Ammonium Salts (62.2).
Circulation and Respiration:

No. 21. Aconite.
Heart, Frog (49):
Mammalian Heart (63.7):
Circulation and Respiration —
  Therapeutic (52.4 — 59.4):
  Toxic (63.7):
Taste (18. B — 43. I — 52.4):
Other Symptoms (52.4):

No. 22. Veratrin.
Muscle (45. I):
Heart, Frogs (49):
  Mammalian (63.8):
Circulation and Respiration (63.8):
General Symptoms and Motor Effects (39. II — 45. I):
Intestinal Canal (32.4):
Mucous Membrane (18. B):

No. 23. Sulphates.
Absorption (63.1):
On Chlorid Excretion (65.1):
On Carbolic Poisoning (59.6):

No. 24. Hemorrhage.
Circulation and Respiration (65.3):
Treatment (65.4 and 5):

No. 25. Muscarin (50. I).
Vagus:

No. 26. Curare.
Muscle-Nerve (42. I — 63.2):
Vagus (63.2):
Circulation and Respiration (63.2):
Treatment (42. I — 63.2):

No. 26a. Magnesium.
General Effects (40. V; 41, V):
Local Effects (43, IV c):
Heart (63, 5):
Absorption (63, 1):

No. 27. Physostigmin.
Peristalsis (67.3):
Pupil (54.1 and 2):
Vagus (50. I):
Muscle-Nerve (42. I):

No. 28. Pilocarpin.
Glands (55.2, 3, and 4):
Pupil (54.1 and 3):
Vagus (50. II — 67.6):

Pilocarpin:
Peristalsis (67.6):
Circulation and Respiration (67.6):

No. 29. Nicotin.
Vagus (50. II — 67.7):
Peristalsis (67.7):
Circulation and Respiration (51.2 — 67.7):
Vessels (51.2):
General Symptoms, Frog (42. II and III):
  Mammals (24. III — 51.2):
Glands (24. III — 55.4):
Pupil (51.2 — 67.7):
Muscle-Nerve (42. II):

No. 30. Atropin.
Glands (52.3 — 55.3 and 4):
Pupil (52.3 — 54.1 — 67.8):
Vagus (50. I — 52.3 — 67.8):
Circulation and Respiration (52.3 — 61.6 — 67.8):
General Symptoms (28.1 — 52.3):
Peristalsis (67.5 and 8):
Idiosyncrasy (28.1):
Antagonism (55.3, etc.):

No. 31. Arsenic.
Alimentary Canal (32.3 — 67.9):
Kidney (33.1):
Blood Pressure (67.9):

No. 32. Salt-Action.
Kidney and Urine (23.3 — 65.1 — 70.1 and 2):
Muscle (46. I and III):
Heart (46. IV):
Nerve (46. II):
Peristalsis (46. V — 67.2):
Blood (22 — 23.2):
Absorption (63.1):

No. 33. Calcium.
Kidney and Urine (70.3):
Muscle (46. III):
Peristalsis (46. V):

No. 34. Citrate.
Kidney and Urine (23.3 — 70.4):
Muscle (46. III):
Peristalsis (46. V):

No. 35. Circulation on Kidney (69 — 70.5).
Arterial Pressure:
Venous Pressure:
Ureter Pressure:

No. 36. Hydrocyanic Acid.
General Symptoms (24. III):
Nerve (43. IV):
Kidney Vessels and Urine (71.2 — 72.5):
Oxidation (72.5):
Hemoglobin (21):

No. 37. Normal Saline Solution.
Circulation and Respiration (58.7 — 62.1 — 65.1):
In Hemorrhage (65.4):
Heart (46. IV):

Normal Saline Solution:
Kidney and Urine (65.1 and 4—72.3):
Absorption (63.1):

No. 38. Nitrites.
Peripheral Vessels (51.5—73.3):
Circulation and Respiration (52.5—59.1):
Hemoglobin (21):
Saliva (27.1):

No. 39. Barium.
Peristalsis (46. V—67.4):
Vessels (71.5—73.6):
Heart (49):
Circulation and Respiration (65.6):
Urine (65.6—71.5):
Muscle (46. III):

No. 40. Suprarenal.
Vessels (27.3—51.4—71.1—73.2):
Heart (49—74.4):
Circulation (and vagus) (58.7—59.2—63.6):
Urine (71.1):
Glycosuria (34.3):
Absorption (24. VII):

No. 41. Potassium.
Heart, Frogs (49):
  Mammalian (74.5):
Muscle (45. I):
Circulation and Respiration (63.5):

No. 42. Camphor.
Motor System (39. III):
Heart (49—74.6):

No. 43. Strychnin.
General Symptoms (24, I, IV, V—29):
Motor System (29—38. I—39. I—74.1—76.1):
Rigor (29.—39 I—74.1):
Heart (49—76.1):
Circulation and Respiration (59.7 and 8—61.7 and 8—63.3):
  Therapeutic:
  Toxic:
Treatment (29):
Taste (43. II):
Infusoria (20.3):
Yeast (20.2):

No. 44. Caffein.
Heart (49.—74.2—76.2):
Circulation and Respiration (29 VI—61.3—63.4):
Urine (65.2—72.4):
Muscle (45.—62.5):

No. 45. Alcohol, Ether, Ethyl Chlorid, Chloroform, Chloral, Urethane, etc.

Central Nervous System, Consciousness, Reflexes, Respiration, General Circulation, etc.—
  Frogs (41. II to IV):
  Mammals (40. II to IV—58—61.1):
  Heart, Frogs (49):
    Mammalian (74.3—76.3):
  Vessels (71.4—73.5):
  Temperature (29. III and VI—36.1):

Alcohol, etc.:
  Cilia (44. I):
  Seeds (44. II):
  Muscle (45. V—65.7):
  Treatment (29. III and VI—58):

No. 46. Digitalis.
 Heart, Frogs (49):
  Mammalian (74.7—75—76.3):
 Vessels (51.3 and 5—71.3—72.6—73.4):
 Circulation and Respiration (62.3): Strophanthus (62.4):
  Therapeutic:
  Toxic:
 Pulse (Man) (52.2):
 Idiosyncrasy (28.2):

CHAPTER XXXIX.

DOSES FOR ANIMALS.

[The drugs are arranged alphabetically; in the case of salts, by the more important ion. In the case of crude drugs, the dose refers to fluid preparations. The "just fatal" doses have generally been worked out with considerable accuracy, but may vary somewhat with different samples of the poison, and with each lot of animals. The doses marked with an asterisk (*) have been confirmed by the author; the others were compiled from pharmacologic literature. Ex. signifies that the drug is used in the experiments of this course. The reference may be located by consulting the guide in Chapter XXXVIII, pages 940 to 945.

ABRIN.—*Rabbit,* 0.01 mg. × Kg., vein, just fatal. *Local, eye:* just causes not dangerous ophthalmitis.

ACETANILID.—*Man,* 0.3 Gm., mouth, indophenol reaction in urine, Ex.* *Dog,* 0.7 Gm. × Kg., stomach, cyanosis and methemoglobinemia, fatal in nine hours. *Rabbit,* 0.2 Gm. × Kg., stomach, slowed heart and respiration, paralysis of legs, recovery in three hours.*

ACETATE SODIUM.—*Man,* 3.6 Gm.: urine becomes alkaline and effervesces with acids in two hours. *Dog,* 35 c.c. × Kg. of 1.94% crystals, vein, not dangerous*; 3 Gm. × Kg., vein, just fatal.[1]

ACID, HYDROCHLORIC.—*Rabbit,* 1 Gm. × Kg., as 1%, stomach, slowed heart and respiration, ascending paralysis, convulsions, death in 12 to 45 min.* *Guinea Pig,* 10 to 50 c.c. of 1%, rectum, slowed heart and respiration, convulsions, fall of temperature, death by respiratory failure in 12 to 45 minutes, early rigor.*

ACID TARTARIC.—*Guinea Pig,* 0.1 Gm. × Kg., as 0.5%, subcutaneous, reduces alkalinity of blood for experimental purposes.

ACID PHOSPHATE SODIUM (or $Na_2HPO_4 + H_3PO_4$ till Congo paper is blued).—10%, intravenously, produces acid-action in dogs or rabbits.

ACOIN.—Local anesthetic, ⅓ to 1%.

ACONITE.—*Dog,* 0.04 Gm. × Kg., subcutaneous, nausea, incoordinated movements, irregular heart and slowed and irregular respiration, convulsions in 25 minutes, death in 34 minutes.* *Anesthetized dog,* 0.015 Gm. × Kg., vein, therapeutic dose, blood pressure, Ex.*. 0.10 Gm. ×

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[1] For fatal dose of a series of Sodium Salts, see Sabbatani.

Kg., vein, fatal (Cardiomyogram) Ex.*. *Anesthetized rabbit*, as dog.* *Guinea Pig*, 1 c.c. of 50%, subcutaneous, fatal in 13 minutes; 1 c.c. of 1:150 subcutaneous, fatal.* *Frog's heart*, local application, 1:25, typical action (Ex.)*.

ACONITIN.—

	PETIT.	MERCK.	FRIEDLANDER.	SOURCE NOT STATED.	
Rabbit, Subcut....	<0.1 mg. × Kg.	<1.5 mg. × Kg.	>6 mg. × Kg.		Just Fatal.
Guinea, Subcut....	0.5 mg. × Kg.	<2. mg. × Kg.	<1.5 mg. × Kg.		Just Fatal.
Pigeon, Subcut....				.06 mg. × Kg.	Just Fatal.
Frog. Subcut....	<0.22 mg. × Kg.				Just Fatal.
Frog	<0.4 m.g	<1. mg.	<200. mg.	4 mg. × Decagr.	Just Fatal.
	0.16 mg. × Decagr.				Just Fatal.

ACROLEIN.— Mammals, 0.15 to 0.2 Gm. × Kg., stomach, just fatal.

ADRENALIN.—$^{1}/_{100}$%, *local vasoconstriction*,* Ex. *Revival of heart*, 50 c. c. × Kg. of 1:50,000 normal salt, vein, Ex.* *Anesthetized Dog*, 0.03 to 0.05 mg. × Kg., vein, ordinary dose, Ex.* (blood pressure). 0.001 causes 14 mm. of rise. *Rabbit*, 1 to 2 mg., subcutaneous, glycosuria in a few hours (Ex.*). 0.4 to 0.5 mg. × Kg., intramuscular, blood pressure. *Fatal Dose: Dog*, 1 to 2 mg. (0.1 to 0.25 mg.) × Kg., vein, 5 to 6 mg. × Kg., subcutaneous; *Rabbit*, 0.4 mg. × Kg., femoral vein; 0.2 mg. × Kg., jugular vein; *Guinea Pig*, 0.1 to 0.2 mg. × Kg., vein; *Cat*, 0.5 to 0.8 mg. × Kg., vein.

AGURIN.— *Rabbit*, 0.4 Gm. × Kg., stomach, diuretic*; 50 mg. × Kg., vein, diuretic, Ex.*.

ALBUMOSE.—*Rabbit*, 3 to 5 c.c. of 20%, subcutaneous, rise of temperature to 40.3° C., Ex.*; *Dog*, 0.3 to 0.6 Gm. × Kg., vein, renders blood non-coagulable (*).

ALCOHOL (ETHYL).—*Man*, 10 Gm., mouth, first increases then decreases muscular work; *Mammals*, 0.25 to 0.75 c.c. in 6 to 25% sol., increases respiration; 25%, vein, does not coagulate blood (*); *Rabbit*, 10 c.c. × Kg of 50%, stomach, paralytic stage, Ex. (Antidote) (*); lowers hyperpyrexia; 2.5 to 4 Gm. × Kg., narcotic, recovery in 1 to 2 hours; 4.5 to 6, recovery in 6 to 10 hours; 6.25 to 7.25, just fatal; *Cat*, 4 c.c. × Kg., peritoneum (as 40%), coma, not fatal (*); 8 c.c (in two doses, 6 hours apart), coma lasting 2½ days, ending in death (*). *Guinea Pigs*, 4 c.c. × Kg., peritoneum, coma, not fatal (*). *Frogs*, 0.3 c.c., subcutaneous, ordinary dose; 0.6 c.c., fatal dose. *Anesthetized Dogs*, 35 c.c. per Kg. of 3%, vein, not fatal (*); 25 c.c. of 50%. stomach, fall of blood pressure, not fatal (*). *Excised mammalian heart*, 0.13 to 0.3%, stimulant; above 1%, depressant.

Alcohols, Higher.—*Rabbit,* stomach, Gm. × Kg.:

	Recovery in 1 to 2 Hours.	Recovery in 6 to 10 Hours.	Just Fatal.
Methyl	3.2 to 5.2	5.6 to 6.9	7.2 to 9.02
Ethyl	2.5 to 4.1	4.45 to 6.15	6.25 to 7.44
Propyl	1.6 to 2.4	2.58 to 2.96	3.0 to 3.46
Butyl	1.0 to 1.5	1.65 to 2.0	2.1 to 2.44
Amyl	0.83 to 1.1	1.25 to 1.66	1.7 to 1.95

Aleuron Suspension.—Subcutaneously, aseptic inflammation in mammals.

Alkaloids.—*Local doses: Eye,* $^1/_{10}$% to 1%; *heart, muscle, and nerve,* $^1/_{50}$ to $^1/_5$% (*).

Aloin.—*Rabbit,* 2 to 4 c.c of warmed 5% aqueous, subcutaneously; temporary, acute diffuse nephritis (*) Ex. Doses above 4 c. c. are apt to be fatal; continued use causes contracted kidney.

Alum.—0.25 to 0.5% introduced into intestine, retards absorption.

Aluminum (calculated as metal).—Just fatal dose, subcutaneously, *Frog,* 12-16 mg.; *Rabbit,* 160 mg. × Kg.; *Cat,* 150 mg. × Kg.; *Dog,* 130 mg. × Kg.

Ammonia, Inhalation.—*Rabbit,* Ex. (*) (Respiration); *Dog,* increased heart rate, slight rise of pressure, slowed but deepened respiration (*).

Ammonium Carbonate.—*Dog,* 20 c.c. of 5%, stomach, emetic Ex.; *Rabbit,* 0.4 Gm. × Kg., subcutaneously, convulsions; *Frog,* 0.025 Gm., subcutaneously, convulsions.

Ammonium Chlorid.—*Anesthetized Dog or Rabbit,* 15 c.c. × Kg. of 1%, vein, increased blood pressure and respiration; sometimes convulsions; recovery (*). Ex. 0.1 Gm. × Kg., vein, increased respiration; 10 to 40 mg. × Kg., vein, little effect (*).

Amyl Nitrite.—*Anesthetized Dog,* inhalation, fall of blood pressure and quickened heart, Ex. (*); *Man,* flushing, increased heart, Ex. (*).

Anesthesin.—Just fatal doses: *Dog,* 0.4 Gm. × Kg., vein; *Rabbit,* 1.15 Gm. × Kg., stomach; *Guinea Pig,* 0.90 Gm. × Kg., peritoneum.

Anilin.—*Frog,* 2 drops in mouth, cause incoordination, convulsions, paralysis, stoppage of heart in 10 minutes (*).

Antiarin.—0.05 to 0.1 mg. (local?) just stops the heart of Rana esculenta, 0.004 of R. temporaria.

Antimony and Potassium Tartrate.—*Dog,* 0.1 to 0.4 Gm., stomach, emetic, Ex. (*); *Rabbit,* 0.15 Gm. × Kg., as 2.5%, vein, fatal in 24 hours.

Antipyrin (as Acetanilid).—*Rabbit,* 0.1 Gm. × Kg., stomach, antipyretic, Ex. (*); metabolism, Ex.

Apocodein Hydrochlorid (Paralysis of nerve-cells and endings, particularly vasomotor).—*Vein,* 40 to 50 mg. × Kg. (as 1%); *local,* 1%; *perfusion,* inject 2 c.c. of 1%.

Apocynum.—*Dog,* 0.2 Gm. × Kg., stomach, emetic (*); *Anesthetized Dog,* 0.35 Gm. × Kg., subcutaneous, slowed heart and rise of blood pressure (*); *Guinea,* 0.1 to 0.25 Gm. × Kg., subcutaneous, no effect; 0.3 to 0.35, paralyzed, but recovery; 0.4 to 0.5, convulsions, death in 2 to 5 hours (*); *Frogs,* 0.5 mg. × Gm., no effect; 1.2 just fatal in 15 hours (*). *Frog's heart,* local, 1 · 50, slows and stops (*).

Apomorphin Hydrochlorid.—*Dog,* 10 mg. (2 mg. × Kg.), subcutaneous, emetic Ex. (*); *Rabbit,* 10 mg., subcutaneous, excitement Ex. (*); *Frog's heart,* 1 : 200, local, slows and paralyzes (*); *White* *rat,* 0.01 mg. × Gm., no effect; 0.1 mg., nausea and retching after 30 minutes, recovery in an hour (*).

Arsenate of Sodium.—*Guinea Pig,* 0.3 mg., subcutaneous, diarrhea in 50 minutes, fatal (*); *Anesthetized Rabbit,* 25 to 50 mg. × Kg., vein, fall pressure, enteritis, Ex. (*). *Rabbit,* 10 mg. × Kg., subcutaneous, nephritis, Ex. (*); 5 c.c. of 5%, subcutaneous, fatal, Ex. (*).

Arsenic (Fowler's Solution).—Stomach, *Rabbit,* 0.6 c.c. × Kg., may be fatal inside of 12 hours; 1.5 c.c. may be survived; *Dog,* 1 c.c. × Kg., vomiting, may be fatal; 3.5 c.c. may be survived; if vomiting is prevented by morphin, 0.5 c.c. to 1 c.c. may be fatal inside of 12 hours.

Aspidospermin.—*Dog,* 2.5 to 8 mg. × Kg., hypodermic or intravenous: increase of respiration.

Atropin Salts.—*Dog,* 0.2 mg. × Kg., subcutaneous; not toxic; effect on pupil and heart (*); 10 mg. × Kg., vomiting (*); 4 to 80 mg. × Kg., severely toxic, but not fatal, Ex. (*); just fatal lies between 20 and 400 mg. *Cat,* hypodermic, mg. × Kg.: 0.02, no effect on pupil; 0.04, good dilatation; 0.05, just paralyzes vagi. *Rabbit,* survives 0.5 to 1 Gm. × Kg., subcutaneous. *Anesthetized Dogs,* 1 mg. × Kg., subcutaneous, paralyzes vagi and dilates pupil; other effects not severe, Ex. (*). *Anesthetized Rabbit,* 10 mg. × Kg., subcutaneous, paralyzes vagi in six minutes; 4 mg. × Kg., vein, still active peristalsis; 10 mg. × Kg., arrests peristalsis, Ex. (*); Local $^{1}/_{10}$% to 1%, dilates pupil, Ex. (*), and arrests peristalsis, Ex. (*). *Guinea Pigs,* 0.5 to 0.7 Gm. × Kg., subcutaneous, just fatal. *Rat,* 2.5 Gm. × Kg., subcutaneous, just fatal; 0.5 Gm., restlessness and excitement; 0.1 Gm., only dilatation of pupil and loss of appetite. *Frog,* 1 mg, little effect; 2 mg. (per 20 Gm.), motor depression with recovery; 10 mg. per 20 Gm., fatal, 50 mg., ordinary dose; 100 mg., fatal (*). *Frog's heart,* local, $^{1}/_{10}$%, paralyzes vagus (*); 1 : 1,000 arrests secretion of mucus from Frog's skin (*).

Barium Carbonate.—*Dog,* 4 Gm., stomach, fatal.

Barium Chlorid.—*Anesthetized Dog,* 20 mg. × Kg., vein, ordinary dose (*). Local, intestine, Ex. (*). *Frog's heart,* 1 : 100, digitalis action. *Perfusion,* Ex. (*).

Belladonna.—*Anesthetized Dog,* 0.05 Gm. × Kg., subcutaneous, ordinary dose.

Benzoic Acid.—*Frog,* 1 mg. × Gm., subcutaneous, toxic; 2.5 mg. × Gm., fatal in 3 hours.

Berberin.—Dog, 2 to 20 mg. × Kg., vein, diminished excitability of vagus. *Frog,* 10 mg., subcutaneous, vagus paralyzed beyond ganglia.

Beryllium (calculated as metal).—Just fatal dose, subcutaneous *Frog,* 8–9 mg. × Kg.; *Cat,* 2 mg.; *Rabbit,* 3 mg.

Bichromate Potassium.—*Dog,* 0.06 to 0.4 Gm., stomach, fatal; *Rabbits,* 30 mg. × Kg., subcutaneous, nephritis in 24 hours, confined almost exclusively to the convoluted tubules, Ex. (*).

Boric Acid.—*Dog,* up to 3 Gm. per day, or Borax to 5 Gm., no effect.

Brucin Hydrochlorid.—Subcutaneous, *Dog,* 4.25 mg. × Kg., exaggerated reflexes ("Schreckhaft"); 4.5, convulsions; 7.5 tetanic. *Rabbit,* 6.25, Schreckhaft; 7.5, convulsive; 8.6, tetanic; 18.5, just fatal. *Pigeon,* 6.0, Schreckhaft; 26.5, convulsive; 42.2, just fatal. *Mouse,* 40.3, convulsive; 108.2, just fatal. *Dog,* per rectum, 4.0, no action; 4.25 to 16.0, Schreckhaft; 17 to 18, tetanic.

Cadmium Salts.—*Dog* (large), 0.03 Gm., subcutaneous, fatal. *Rabbit,* 0.02 to 0.04 Gm., Stomach, fatal. *Frog,* 1 mg. × Gm., fatal.

Caffein Citrated.—*Man,* 0.1 Gm., for ergograph; 0.50 Gm., maximal diuretic. *Dog,* 1 Gm. × Kg., hypodermic, fatal. *Anesthetized*

Dog, 10 mg. × Kg., subcutaneous, diuretic (*); 10 mg. to 20 mg. × Kg., vein, accelerated heart, without increase of strength, Ex. (*), (myocardiogram), respiration increased; 20 mg. often tremors; 50 mg. × Kg., vein, acceleration of heart with weakening of auricles (*); 100 to 200 mg. × Kg., vein, tetanus, weakening of heart; often death (*); into artery, 10 c.c. of 1%, rigor (*). *Rabbit,* about as for Dog; 4 to 10 mg. × Kg., stimulates vagus center; 30 mg. × Kg., subcutaneous, increased respiration, Ex. (*); 20 mg. × Kg., subcutaneous; antidote to alcohol, Ex. (*). *Frog,* 10 mg., ordinary dose (toxic rigor), Ex. (*); fatal dose, 15 mg. (*). *Frog's Muscle and Heart,* Ex., $^1/_{20}$ to 1% (*).

CALABARIN.—*Rabbit,* 20 mg. × Kg., subcutaneous, convulsions, fatal.

CALCIUM CHLORID.—*Dog,* 1 Gm. × Kg., vein, ordinary dose. *Frog's muscle,* ¾%, paralyzes (*).

CALOMEL.—*Dog,* 0.4 Gm., stomach, therapeutic dose. *Rabbit,* 5 to 10 mg. × Kg., subcutaneous or vein, diuresis without albuminuria; death by gastroenteritis (dissolved in sodium hyposulphite, 1 c.c = 5 mg.).

CAMPHOR.—*Rabbit,* 2 Gm. in oil, subcutaneous or stomach, convulsions, Ex. (*); 5 Gm., periodic rise and fall of blood pressure; vein, 1 to 2 c.c. of solution of camphor 1, alcohol 40, water to 100, cardiac effect. *Dog,* 4 Gm. in oil, stomach, convulsions (*). *Frogs,* 0.1 Gm., subcutaneous, paralyses, fatal. *Perfusion of heart,* 2 to 15% of the saturated solution.

CANE SUGAR.—*Rooster,* 10 gm. × Kg., into pectoral muscles, bluing of comb in ¼ to ½ hour.

CANNABIS INDICA.—*Dog,* 1 Gm. × Kg., stomach, ordinary dose, Ex. (*); subcutaneous, little effect (*). *Anesthetized Dog,* 1 Gm. × Kg., subcutaneous, quickened heart and rise of pressure (*). *Rabbits, Guinea Pigs, and Frogs,* above dose has practically no effect (*).

CANTHARIDIN.—*Man,* 0.15 mg., local, vesicant; 0.2 mg., stomach, albuminuria; 30 mg., stomach, fatal. *Dog,* 10 mg., fatal. *Dog or Rabbit,* 5 mg. × Kg. (in acetic ether), hypodermically albuminuria in ten minutes, nephritis involving all structures, Ex. (*); 0.1 to 1 mg. × Kg., slight nephritis involving only glomeruli.

CARBOLIC ACID.—*Dog,* 2 to 3 Gm. × Kg., subcutaneous, just fatal (immediate convulsions, collapse, fall of temperature). *Cat,* 0.09 Gm. × Kg., as 2.5%, subcutaneous, just fatal. *Rabbit,* 0.1 Gm. × Kg., hypodermic, toxic; 0.55 to 0.6 Gm. × Kg., stomach or subcutaneous, surely fatal in ½ to 2½ hours. *Guinea Pig,* 0.4 to 0.55 Gm. × Kg., subcutaneous, just fatal. *White Mice,* 0.35 to 0.6 Gm. × Kg., subcutaneous, just fatal. *Frogs,* 1 to 6 mg. × Dgm. (as 5%), subcutaneous, just fatal. *Guinea Pigs,* intraperitoneal, 0.5 Gm. × Kg. (as 2.5%), just fatal in 10 to 20 minutes, 0.25 Gm. in 36 to 48 hours. *Frogs,* placed in 1:5,000 to 1:1,000, fatal (*). *Anesthetized Dog,* 50 mg. × Kg., vein, toxic effects, Ex. (blood pressure) (*); stomach, 1 c.c. × Kg., concentrated or dilute, severe fall of blood-pressure, death after several hours, recovery by lavage (*).

CARBON DISULPHID.—Inhalation, like chloroform.

CATHARTICS.—*Dog.* Ex. 31.

CEPHÆLIN.—*Man,* 5 to 10 mg., mouth, emetic. *Mammals,* 30 mg. × Kg., subcutaneous, just fatal. *Dog,* 1 mg. × Kg., stomach or subcutaneous, just emetic in ½ to 2 hours.

CERIUM (calculated as metal).—Just fatal, subcutaneous, *Frog,* 15 to 20 mg. *Rabbit,* 20 to 25 mg.

CEVADIN (*).—*Rabbit,* subcutaneous, 6 mg. × Kg., largest dose with recovery; 3 mg. × Kg., smallest dose with death (pain, nausea, rapid respiration, leaps, convulsions, death in 20 minutes to four hours by paralysis of respiration); stomach, 10 mg. × Kg., fatal in 33 minutes to several days, corrosion of stomach.

Guinea Pig, same effects, 3 to 6 mg. × Kg., fatal in 17 to 43 minutes.

Chloral.—*Dog,* stomach, 6 Gm., anesthetic. *Cat,* stomach, 0.15 Gm. × Kg., just fatal. *Rabbit,* 0.3 Gm. × Kg., rectum, anesthetic, Ex. (*); 0.6 Gm. × Kg., stomach, anesthetic, Ex. (*) (Antidote, Ex. (*)); Temperature, Ex. (*); 0.6 Gm. × Kg., stomach, to obtain diuretic effect of caffein. *Frog,* subcutaneous, 0.05 Gm., narcosis; 0.1 Gm., fatal. *Anesthetized Dog,* 0.5 Gm. × Kg., vein, fall of pressure and temperature, weakened and quickened heart (*).

Chlorate of Potassium.—*Rabbit,* 4 Gm. × Kg., stomach, dies in 4 hours after convulsions, with respiratory paralysis; blood brown.

Chloretone.—*Dog,* 60 to 300 c.c. of saturated watery solution, stomach, after morphin, anesthetic; 0.2 to 0.25 Gm. × Kg., mouth, 1½ hours before operation, anesthetic; 0.02 Gm. × Kg., of morphin hypod. and 0.2 Gm. × Kg. chloretone in alcohol by stomach, after morphin vomiting, anesthetic. *Rabbit,* 16 c.c. of saturated watery solution × Kg., rectum, anesthetic, often fatal (*); 0.25 Gm. × Kg. in alcohol, rectal, fatal in 4 hours; 0.15 Gm. × Kg., anesthetic dose. *Anesthetized Dog,* 0.5 c.c. × Kg. of saturated watery solution, vein, weakened heart, quickened rate, fall of pressure (*).

Chlorid of Sodium (*).—0.9%. *Anesthetized Mammals,* 25 to 100 c.c. × Kg. (warm), vein, ordinary dose, blood pressure, respiration, Ex.; diuresis, Ex. (*).

Chlorid of Sodium (*).—10 to 33% (saturated) solution: *Anesthetized Mammals,* vein, death in 4 to 5 minutes, after 10 to 30 c.c. × Kg.

Chloroform.—*Frog,* subcutaneous, 0.3 c.c. ordinary dose; 0.45 c.c. fatal dose; rigor, 5 c.c. peripherally into femoral vein of *mammals* (*).

Chloroform (*).—Saturated solution in normal salt: *Mammals,* 2 to 5 c.c. × Kg., vein, slowing and weakening of heart, larger doses paralysis. See Gréhant anesthesia, index. *Frog's Heart,* Ex. (*), saturated solution stops.

Chromate of Potassium.—*Rabbit,* 0.2 to 0.4 Gm., subcutaneous, or 2 Gm., stomach, fatal. *Birds* (artificial deposit of uric acid): *Pigeons,* 10 mg. *Hens,* 10 to 20 mg., subcutaneous, repeated several days.

Cinchonidin (*).—*Frog,* 0.03 Gm., subcutaneous, paralyzes in some hours without convulsions.

Citrate Sodium (crystals).—*Dog,* vein, 0.37 Gm. × Kg., just fatal. *Frog,* subcutaneous, 4 to 5 mg. × Gm., just fatal.

Cobalt Nitrate.—Subcutaneous, *Rabbit, Dog, Cat,* 40 mg. × Kg., some paresis and urinary changes; 50 to 75 mg. × Kg., just fatal. *Pigeon,* 5 to 10 mg. × Kg., just fatal. *Frog,* 18 to 40 mg. × Dgm., just fatal.

Cocain Hydrochlorid.—*Dog,* subcutaneous, 2.5 mg. × Kg., raises temperature by 0.2 to 0.5° C. for 2 hours; 10 mg. × Kg. by 1 to 2° for 3 to 4 hours; 20 mg. × Kg., 2 to 4° for 6 to 7 hours; 15 to 20 mg. × Kg., emesis, mydriasis, convulsions and paralysis, with recovery; 25 mg. × Kg., sometimes fatal; 80 mg. × Kg., sometimes recovery. *Rabbits,* subcutaneous, 20 mg. × Kg., ordinary dose for hyperpyrexia, Ex. (0.25 to 0.8° in 1 to 3 hours) (*); 30 mg. × Kg., slight, trembling; 50 mg. × Kg., considerable rise of temperature; 60 mg. × Kg., convulsions, paralysis, recovery; 100 mg. × Kg., sometimes fatal; 130 mg. × Kg., sometimes recovery; 540 mg. × Kg., surely fatal. *Guinea Pig,* 60 mg. × Kg., subcutaneous, just fatal. *Frog,* subcutaneous, 0.5 mg., ordinary dose; 3 mg., fatal. *Local,* 1%, vasoconstriction, Ex. (*); temporary paralysis of nerve-trunk, Ex. (*). *Eye,* 1%, Ex. (*).

Cocculus.—*Dog,* 0.4 Gm. × Kg., subcutaneous, fatal. *Frog,* 2 mg. × Gm., ordinary dose.

Codein.—*Rabbit,* 10 mg. × Kg., subcutaneous, maximum therapeutic effect on respiration; 60 mg. × Kg., subcutaneous, just fatal.

Colchicum Root (*).—*Dog,* stomach, 0.25 Gm. × Kg., vomiting and diarrhea; 1 Gm. × Kg., fatal, Ex. (*). *Guinea Pig,* 0.25 Gm. × Kg., subcutaneous, just fatal (*).

Colchicum Seed (*).—One-half the above.

Coniin.—Subcutaneous, *Cat,* 0.4 Gm., fatal inside of one hour; 0.05 Gm. in 9 hours. *Rabbit,* 90 mg. × Kg., fatal. *Pigeon,* 40 mg. × Kg., fatal. *Mouse,* 75 mg. × Kg., fatal (the paralytic dose is about ¾ of the fatal).

Conium (*).—Subcutaneous, *Dog,* 0.5 Gm. × Kg., no effect. *Guinea Pig,* 0.5 Gm. × Kg., just fatal. *White Rat,* 40 Gm. × Kg., just fatal. *Frog,* 0.06 Gm. × Gm., just fatal. *Anesthetized Rabbit,* 5 Gm. × Kg., slight effects. *Frog's heart,* 1 : 10, local, arrests.

Convallaria (*).—Subcutaneous, *Guinea Pig,* 0.08 Gm. × Kg., just fatal. *Rat,* 32 Gm. × Kg., just fatal. *Frog,* 0.26 mg. × Gm., just fatal. *Frog's heart,* local, 1 : 50, digitalis action.

Copaiba.—*Man,* urine, 1.0 Gm. Ex. (*).

Copper Salts (Copper-sodium tartrate).—Fatal doses (as CuO): *Frog,* ½ to 3 mg.; *Rabbit,* 50 mg. subcut., 10 to 15 mg., vein. *Dog,* 0.4 Gm. subcut.; 25 mg., vein.

Copper Sulphate (*).—*Dog,* 50 c.c of 1%, stomach, vomiting in 12 min., Ex.

Coriamyrtin.—Subcutaneous (convulsions), *Dog,* 0.15 mg. × Kg., recovers. *Cat,* 0.25 mg. × Kg., fatal. *Rabbit,* 0.75 mg. × Kg., recovery. *Guinea Pig,* 2.5 mg. × Kg., fatal. *Frog,* 0.1 mg., fatal.

Cornutin Citrate.—Subcutaneous, *Dog,* 3 to 4.5 mg. × Kg., trembling, recovery; 0.5 mg. × Kg., vomiting, diarrhea, paralytic symptoms. *Cat,* 7 mg. × Kg., recovery. *Guinea Pig,* 15 mg. × Kg., convulsions, recovery. *Rabbit,* 0.1 mg. × Kg., vein, rise of blood pressure; 30 mg. × Kg., convulsions, death.

Curare.—*Anesthetized Mammals,* 1 c.c. of ½% × Kg., vein, every 10 minutes, Ex. (*). *Frogs,* 0.1 to 50 mg., subcutaneous, Ex. (*).

Curarin.—*Anesthetized Mammals,* 0.5 to 3 mg. × Kg., vein. *Frog,* subcutaneous, 0.00025 to 0.001 mg. × Gm., normal dose.

Cyanid of Potassium.—*Man,* 0.05 Gm., mouth, fatal. *Rabbit,* 1.9 mg. × Kg., subcutaneous, just fatal; less than 1 mg., no effect. *Pigeon,* subcutaneous, 1.5 to 2.4 mg. × Kg., just fatal. *Mouse,* 4.4 mg. × Kg., subcutaneous, just fatal.

Cytisin.—*Cat,* 30 to 40 mg., subcutaneous, fatal.

Delphinin (Heyl).—*Dog or Cat,* 0.03 to 0.1 Gm., fatal. *Rabbit,* 75 mg. in 5% solution (1.5 c.c.) paralyzes vagus endings without acting on heart-muscle or depressor.

Digitalis.—*Dog,* 0.2 Gm. × Kg., subcutaneous, slowing of heart (*). *Guinea Pig,* 0.2 to 3 mg. × Kg., subcutaneous, just fatal (*). *Frog,* 0.4 mg. × Gm., into thigh, causes systolic standstill in 2 hours; 0.7 to 10 mg. × Gm., subcutaneous, just fatal (*); 0.4 c.c. of Tr. subcutaneous, constricts vessels of foot, Ex. (*). *Anesthetized Mammals,* 0.4 Gm. × Kg., vein (as 4% infus.), ordinary dose, all stages, Ex. (*). *Frog's heart,* local, 2% to 10%, arrests, Ex. (*). *Perfusion,* Ex. (*).

Digitalin or Digitoxin.—*Anesthetized Dog,* 1 to 5 mg. × Kg., vein, all stages. *Frog,* 3 mg., subcutaneous, fatal.

Dionin.—*Rabbit,* subcutaneous, 6 mg. × Kg., maximum therapeutic effect on respiration: 100 mg. × Kg., fatal; conjunctiva, 10% or powder, edema, Ex.

Diuretin.—See Theobromin.

Elaterium.—*Dog,* 4 mg., stomach, no effect (*).

Emetin.—*Man,* 10-20 mg., mouth, emetic. *Dog,* 1¼ mg. × Kg., subcutaneous, just emetic. *Mammals,* 0.1 Gm. × Kg., subcutaneous, or 0.02

Gm. × Kg., vein, fatal in 15 to 20 minutes. *Frog,* 5 mg., paralysis; 10 mg. to 20 mg, fatal. *Local,* Dog's conjunctiva, 1 : 500 irritant.

Ergot (*).— *Rooster,* 2 to 5 Gm., mouth or subcutaneous, blackening of comb in ½ to 2 hours, Ex. (*). *Guinea Pig,* 8 Gm. × Kg., subcutaneous, just fatal. *Frog,* 50 mg. × Gm., subcutaneous, just fatal. *Anesthetized Dog,* 0.02 to 0.04 Gm. × Kg., vein (therapeutic dose); fall of blood pressure, with compensatory rise to a trifle above normal, (*) Ex.

Ether.—*Dog,* anesthesia, Ex. (*). *Anesthetized Dog,* hypodermic, 5 c.c., slight fall of blood pressure (*). *Frog,* hypodermically, ordinary dose, 0.3 c.c.; fatal dose, 0.6 c.c.. *Frog's heart,* Ex. (*).

Eye.— Alkaloids on, local, $^1/_{10}$ to 1%, Ex. (*).

Ferrocyanid of Sodium.— *Dog,* vein, 35 c.c. × Kg., of 7.43% crystals, not fatal (*).

· Fluorid of Sodium.— *Dog,* 0.05 to 0.1 Gm. × Kg., vein, or 0.15 Gm. × Kg., hypodermic, just fatal. *Rabbit,* 0.25 Gm. × Kg., mouth, salivation; 0.5 Gm. × Kg. by stomach or 0.15 subcutaneous, or 0.14 by vein, just fatal. *Frog,* 40 mg., subcutaneous, fatal. *To kill epithelium,* 0.03 to 0.3%. *Preservative,* 0.2%.

Formaldehyd.— *Rabbit,* 0.24 to 0.5 Gm. × Kg., subcutaneous, just fatal. *Blood,* 1 : 400 prevents clotting and spontaneous laking.

Gas.— Inhalation, Ex. (*).

Gasolin.— Inhalation, convulsions, and anesthesia (asphyxia?).

Gelseminin Hydrochlorid.— *Frog,* 20 mg., subcutaneous, increased reflexes, abolition of voluntary movement.

Gelsemium (*).— Subcutaneous, *Guinea Pig,* 1.75 to 6 Gm. × Kg., just fatal; *White Rat,* 2.2 Gm. × Kg., just fatal; *Frog,* 6.5 to 15 mg. × Gm., just fatal; *Frog's heart,* local, 1 : 50, paralysis.

Glucose.— *Dog,* 35 c.c. × Kg. of 2.57%, vein, not dangerous (*).

Glycerin.— *Frog,* 0.5 to 1 c.c. hypodermic, muscular effect.

Gold (calculated as metal).— Just fatal dose, Gm. × Kg., subcutaneous: *Dog,* 0.40. *Cat,* 0.45. *Rabbit,* 0.36. *Frog,* 0.30.

Guanidin.— *Frog's muscle,* local, 1%, fibrillary twitchings (*).

Heart.— Excised Mammalian, Ex.

Proportion of drugs to be added to a liter of the perfusing fluid: Alcohol, 20 c.c.; Caffein, 0.3 Gm.; Chloroform, 0.6 Gm.; Digitoxin, 5.0 mg.; Ether, 1 Gm., no effect; 3 Gm., considerable effect; Strophanthin, 0.8 mg.; Theobromin, 0.5 Gm.

Hedonal.— *Rabbit,* 1 Gm. × Kg., rectum, fatal in 30 minutes (*).

Helleborein.— *Frog,* 0.04 mg. × Dgm., subcutaneous, just systolic standstill. *Toad,* 1.85 to 2.44 mg. × Dgm., same effect. *Local,* heart or muscle, $^1/_{10}$ to ½%.

Helleborus Niger (*).— Subcutaneous, *Guinea Pig,* 0.2 Gm. × Kg., just fatal. *White Rat,* 20 Gm. × Kg., just fatal. *Frog,* 0.3 mg × Gm., just fatal. *Frog's heart,* local, 1 : 50, digitalis action.

Heroin.— *Rabbit,* 0.5 mg. × Kg., subcutaneous, therapeutic effect on respiration, Ex. (*).

Hirudin (Sachsse & Co., Leipzig).— 0.05 Gm. × Kg., *Rabbit,* vein: blood non-coagulable for four hours.

Hydrastin.— *Dog,* ordinary dose, vein, 1 mg. × Kg., Ex. Full dose, 10 mg. × Kg., not fatal. Frog, 1 to 2 mg., subcutaneous, spinal convulsions.

Hydrastinin.— *Dog,* 0.5 to 1 mg. × Kg., vein, rise of pressure, Ex. (*); 10 to 20 mg. × Kg., tetanus and paralysis. *Frog,* subcutaneous, ordinary dose, 5 mg.; fatal dose, 15 mg. *Local,* $^1/_{10}$% vasoconstriction, Ex. (*).

Hydrastis.— 50 times the dose of hydrastin. *Dog,* 0.02 Gm. × Kg., vein, ordinary dose, Ex. (*). 0.25 Gm. × Kg., vein, vagus standstill.

Hydrazin Sulph.—*Rabbit,* 0.2 Gm. × Kg., subcutaneous, no effect; 0.315, convulsions, fatal in ½ hour.

Hydrocotarnin Nitr.—*Rabbit,* 0.2 Gm. × Kg., subcutaneous, just fatal.

Hydrocyanic Acid $\left\{\frac{26.83}{64.65}\right.$ of Cyanid of Potassium.)—*Rabbit,* stomach, 0.1 Gm. (5 c.c. of 2%), fatal, Ex. (*).

Hyoscin.—Subcutaneous, not fatal, *Dog,* 0.03 Gm. × Kg.; *Rabbit,* 0.25 Gm. × Kg.; *Frog,* 25 mg.

Hyoscyamin.—*Cats,* hypodermic, mg. × Kg.: 0.01 mg., no effect on pupil; 0.02 mg., good dilation; 0.025 mg., just paralyzes vagi. *White Mice,* of 12-15 Gm., hypodermic; 5 mg., no distinct symptoms; 10 mg., intoxication, with recovery; 20 mg., fatal. *Frogs,* of 20 gm., hypodermic; 1 mg., no effect; 2 mg., motor depression with recovery; 10 mg., fatal.

Hyoscyamus (*).—Subcutaneous, just fatal, *Guinea Pig,* 10 Gm. × Kg. *Frog,* 10 mg. × Gm.

Hyposulphite of Sodium.—*Rabbit,* 1.5 to 2 Gm. × Kg., subcutaneous, just fatal.

Iodid of Sodium.—*Anesthetized Dog,* 35 c.c.× Kg. of 2.2%, vein, no serious effects (*). *Man,* 0.3 Gm., mouth, in urine, Ex. (*). *Rabbit,* 50 c.c. of 1%, stomach, slight depression, Ex. (*).

Iodin.—*Rabbit,* 2 c.c. of tincture, hypodermic, fever; 0.075 Gm. × Kg., subcutaneous, fatal, ecchymoses in stomach.

Iodoform.—*Rabbit,* 2 Gm. × Kg., in oil, subcutaneous, hypnotic; 1 to 2 Gm., stomach, fatal.

Ipecac.—*Dog,* 0.2 to 0.3 Gm. × Kg., stomach, just emetic, Ex. (*). *Anesthetized Dog,* 1 Gm. × Kg., subcutaneous, increased heart and respiration, fall of pressure, slight intestinal congestion, no peristalsis (*).

Iron (calculated as metal).—Just fatal dose, mg. per animal, subcutaneous: *Dog,* 2-50; *Rabbit,* 25; *Frog,* 5-10 mg. × Kg.

Juniper Oil.—*Anesthetized Dog,* 25 c.c × Kg. of 0.4% suspension, vein, diuretic, no serious effects.

Laudanin.—*Rabbit,* 30 mg. × Kg., subcutaneous, just fatal; 20 mg. × Kg., subcutaneous, convulsions, recovery. *Dog,* 30 mg. × Kg., subcutaneous, convulsions, death.

Laudanosin.—*Rabbit,* 65 mg. × Kg., subcutaneous, not fatal; 68 just fatal.

Leech Extract.—*Mammals,* 3 heads per Kg. in 6 c.c. of normal salt, vein, prevents coagulation.

Lobelia (*).—Subcutaneous, just fatal, *Guinea Pig,* 10 Gm. × Kg.; *Frog,* 55 mg. × Gm.; 1:25, *local,* paralyzes vagus ganglia in Frog's heart; *Anesthetized Dog,* subcutaneous, 0.012 Gm. × Kg., little effect; 0.33 Gm. × Kg., heart first slowed, then quickened.

Lobelin Sulphate.—Subcutaneous, *Rabbit,* 2 mg. × Kg., increases respiration; *Pigeon,* 54 mg. × Kg., just fatal; *Frog,* 3 mg., increases and then depresses reflexes.

Magnesium Sulphate (crystals).—Anesthetic dose, hypodermic, all animals, 1.5 Gm. per Kg., as 25% solution; fatal, 2 Gm. per Kg.; Ex. Intraspinal, 1 c. c. of 25%, per 10 Kg. Local, 1 to 25%.

Manganese (calculated as metal).—Just fatal dose, subcutaneous, mg. × Kg.: *Dog,* 10-13; *Cat,* 6-7; *Rabbit,* 5 to 6; *Frog,* 2.

Mercuric Chlorid.—*Dog,* 10 c.c. of 1:1,000, subcutaneous, daily, nephritis, mainly interstitial, Ex. (*). *Rabbit,* 25 c.c. of 1%, stomach, fatal in 3 hours, corrosion of alimentary canal, Ex. (*); 1 c.c. of 1%, subcutaneous fatal. *White Rat,* 5 c.c. of 1%, subcutaneous, fatal in 3½ hours (*). *Frog,* local, 1:10,000, to exposed mesentery, prevents emigration of leucocytes.

Methyl Coniin.—*Mouse,* 102 mg. × Kg., subcutaneous, just fatal

(97% of this paralyzes, 30% convulsions). ***Pigeon,*** 54 mg. × Kg., subcutaneous, just fatal.

Methylen Blue.—*Man,* 0.1 Gm., mouth, urine, Ex. (*). ***Anesthetized Dog,*** 25 c.c. × Kg. of 0.5%, vein, fatal.

Morphin Salts.—*Dog,* 5 mg. × Kg., subcutaneous, causes vomiting, but after this prevents action of emetics; 10 to 150 mg. × Kg., subcutaneous, fall of temperature by about 2° C., maximal in 2 hours; 20 mg. × Kg., subcutaneous, ordinary dose, slowing of heart and respiration, Ex. (*); 0.2 to 0.5 Gm., vein, not fatal. *Cat,* 40 mg. × Kg., excitement, Ex. (*). *Rabbit,* subcutaneous, 2.5 to 10 mg. × Kg., maximal therapeutic effect on respiration, Ex. (*); 20 mg., inhibits ascending peristalsis after application of NaCl; reappears with 60 mg.; 50 mg. × Kg., subcutaneous, surgical anesthesia, glycosuria, Ex. (*); 0.1 Gm. × Kg., subcutaneous, fall of temperature, Ex. (*); 0.15 to 0.3 Gm. × Kg., just fatal in 2 to 24 hours; stomach, 0.5 Gm. × Kg., narcotic, 0.7 to 1 Gm. × Kg., fatal. *Guinea Pig,* 0.7 Gm. × Kg., just fatal, Ex. (*). *White Rat,* 0.45 Gm. × Kg., just fatal. *Frog,* 0.05 Gm., paralysis, secondary tetanus in ½ to 1½ hours, fatal (*).

Muscarin.—*Dog,* 2 mg. × Kg., subcutaneous, for heart effect. *Cat* (sulphate, hypodermic, dose per animal); ½ to 1 mg., severe intoxication, but recovery; 1 mg., complete blocking of bronchioles; 3 to 4 mg., death in 2 to 12 hours; 8-12 mg., death in 10 to 15 minutes. *Frog,* 0.5 mg., subcutaneous, vagus standstill; 0.6 mg. fatal. *Local,* 0.1 to 0.2%, Ex. (*). *Local to Rabbit's Intestine,* $^1/_{10}$%, starts peristalsis, spreading up and down; arrested by 1% atropin. *Frog,* 0.12 to 0.23 mg. × Dgm., just fatal. *Toad,* 0.21 to 0.27 mg. × Dgm., just fatal.

Mustard.—*Dog,* emetic, teaspoonful, stomach, Ex.

Naphthol β.—*Dog,* stomach, therapeutic dose, 0.05 Gm. × Kg. ***Cat,*** 0.01 Gm. × Kg.; fatal dose, 0.1 Gm. × Kg.

Narcotin.—*Dog,* 0.05 Gm. × Kg., subcutaneous, slight narcosis. ***Cat,*** 3 Gm., fatal. *Frog,* 50 to 70 mg., some action.

Nickel.—*Rabbit,* same dose and effect as Cobalt.

Nicotin.—*Dog,* few drops on tongue, convulsions, generally recovery, Ex. (*); 0.05 to 0.1 Gm., subcutaneous, fatal. ***Rabbit,*** mouth, as dog (*); subcutaneous, 20 mg. × Kg., just fatal (*); 7 to 10 mg., vein, blocks sympathetic; 10 mg. × Kg., subcutaneous, vessels, Ex. (*). *Guinea Pigs,* subcutaneous, just fatal, young, 14 to 20 mg. × Kg.; adult, 40 to 45 mg. × Kg. *Frogs,* 2 mg., fatal, Ex. (*). *Local,* frog's heart, $^1/_{10}$%, Ex. (*). *Intestine,* 1%, contracture relieved by atropin (*). ***Anesthetized Dogs,*** 2 to 10 mg. × Kg., subcutaneous, vagus stimulation with secondary paralysis, effect on respiration, Ex. (*); 5 mg. × Kg., vein, paralysis of ganglia; same dose for cat. ***Frog's Muscle-Nerve,*** 0.1%, Ex. (*).

Nitrate of Sodium.—*Anesthetized Dog,* 75 c.c. × Kg. of 1.25%, vein, no serious effects (*). *Frog,* 0.03 Gm., fatal.

Nitrite of Sodium.—*Rabbit,* 10 mg. × Kg., subcutaneous, fatal (gastritis, central paralysis, methemoglobin). *Guinea Pig,* 5 c.c. of 3%, subcutaneous, fatal. *Frog,* 0.55 mg. × Gm., subcutaneous, stimulation of cord not effective, fatal in one hour by paralysis. ***Perfusion,*** Ex. (*).

Nitroglycerin.—*Anesthetized Dog,* 1 mg. × Kg., subcutaneous, quickened heart, fall of blood pressure (*).

Oxalate of Sodium.—*Dog,* 0.2 Gm., subcutaneous or stomach, not fatal, causes indicanuria; 0.12 Gm. × Kg., vein, just fatal. ***Rabbit,*** 0.250 Gm., subcutaneous, just fatal in some hours, oxalate deposit in kidneys, Ex. (*). *Cat,* 0.375 Gm., subcutaneous, just fatal. ***Guinea Pig,*** 0.4 Gm. × Kg., subcutaneous, fatal in some hours (*). ***Chicken,*** 0.5 Gm. × Kg., subcutaneous, just fatal. *Turtle,* 0.26 Gm. × Kg., subcutaneous, just fatal. *Frog,* 0.5 mg. × Gm., subcutaneous, just fatal.

Blood, 0.2 to 1:300, prevents coagulation; 1.5% practically isotonic with mammalian blood.

OXALIC ACID.—*Rabbit,* 2 to 4 Gm., stomach, fatal in ¼ to ½ hour. *Guinea Pig,* 0.1 Gm., subcutaneous, fatal. *Frog,* 0.04 to 0.08 Gm., subcutaneous, heart standstill.

OXYDIMORPHIN.—*Dog,* 0.06 Gm. × Kg. (dissolved in 0.2% NaOH), vein, just fatal; subcutaneous, not fatal in any dose.

PARALDEHYD.—*Rabbit,* 3 Gm., stomach (to paralyze vasomotors) (per animal); 1 Gm. × Kg., anesthetic.

PAPAVERIN HYDROCHLORID.—*Man,* therapeutic dose, 0.03 to 0.05 Gm.

PERMANGANATE OF POTASSIUM.—*Rabbit,* 15 c.c. × Kg. of 1%, stomach, alkaloidal antidote, Ex. (*); 0.2 Gm. × Kg., severe gastritis; 0.6 Gm. × Kg., fatal. *Dog,* stomach, 0.1 Gm. × Kg., severe gastritis; 0.4 Gm. × Kg., fatal.

PERONIN.—*Rabbit,* 15 mg. × Kg., subcutaneous, maximum therapeutic effect on respiration.

PHENACETIN.—*Man,* 0.3 Gm., mouth, indophenol reaction, Ex. (*). *Dog,* 0.3 Gm. × Kg., stomach, narcosis, cyanosis, death in 6 hours.

PHENOL.—See Carbolic Acid.

PHENYLHYDRAZIN SALTS.—*Rabbit,* 0.14 Gm. × Kg., subcutaneous, death in 20 minutes; 0.07 Gm. × Kg., death on second day; methemoglobinemia.

PHLORRHIZIN.—*Dog,* 0.3 mg. × Kg., subcutaneous, just sufficient to cause some diabetes; 0.15 Gm. × Kg., subcutaneous, maximal diabetes in starving animals; 0.1 Gm. × Kg., vein, not dangerous (*). *Rabbit,* about same; 0.25 Gm., subcutaneous, ordinary dose, Ex. (*).

PHOSPHATE OF SODIUM.—*Dog,* 35 c.c. × Kg. of 5.1% crystals, vein, not dangerous.

PHOSPHORUS (in oil or mucilage).—*Dog,* 20 mg. × Kg., stomach, fatal. *Rabbit,* 3 to 7 mg. × Kg., stomach, fatty degeneration. *Frog,* ¼ mg., mouth, fatty degeneration.

PHYSOSTIGMA.—*Rabbit,* 0.5 to 1 Gm., fatal.

PHYSOSTIGMIN SALTS.—*Dog,* 4 to 5 mg. × Kg., subcutaneous, just fatal. *Cat,* 3 mg. × Kg., subcutaneous, just fatal. *Rabbit,* 3 mg. × Kg., subcutaneous, just fatal in six minutes (fibrillary twitchings). *Guinea Pig,* 5 mg. × Kg., subcutaneous, just fatal. *Frog,* 0.5 mg., subcutaneous, slows and strengthens heart; usually fatal (*). *Anesthetized Dog,* 0.5 to 2 mg. × Kg., subcutaneous, slower and stronger heart, rise of pressure, intestines contracted (*); removes effect of curare. *Anesthetized Rabbit,* 1 mg. × Kg., vein, increases respiration. *Local,* 1%, Eye, Ex. (*); Intestine, Ex. (*). *Frog's Muscle,* 1:500, height of contraction and irritability increased; 1%, thin strips, fibrillary contractions. *Frog's heart,* 0.1%, Ex. (*).

PICRIC ACID.—*Rabbit,* 0.15 Gm. × Kg., vein or 0.2 Gm. × Kg., subcutaneous, fatal.

PICROTOXIN (convulsions and paralysis).—*Dog,* 1.5 mg. × Kg., subcutaneous, just fatal; 1.1 to 1.4 mg. × Kg., or 1.05 to 3.7 mg. × Kg., rectal, convulsions; 0.5 mg. × Kg., subcutaneous, or 0.55, rectal, salivation; 0.475 mg. × Kg., subcutaneous, or 0.525, rectal, no effect; 11 mg. × Kg., subcutaneous, convulsions in 18 minutes, death in one hour; 0.06 Gm., stomach, fatal in an hour. *Cat,* 1 mg. × Kg., subcutaneous, convulsions, recovery. *Guinea Pig,* 5 mg. × Kg., subcutaneous, convulsions, recovery; 16 mg., subcutaneous, fatal. *Frog,* 2 to 4 mg., subcutaneous, active; 10 mg. fatal, Ex. (*); 4.9 mg. × Kg., subcutaneous, just convulsive. *Toad,* 9 to 9.6 mg. × Kg., subcutaneous, just convulsive. *Anesthetized Dog,* 1 mg. × Kg., subcutaneous, slowed heart with rise of pressure; larger doses, quickened heart, and fall of pressure (*).

PILOCARPIN SALTS.—*Rabbit or Dog,* 5 mg. × Kg., subcutaneous, salivation, Ex. (*). *Rabbit or Rat,* hypodermic (?), just fatal dose, 0.35

Gm. × Kg. *Guinea Pig,* 0.04 to 0.046 Gm. × Kg., just fatal. *Hedgehog,* 0.02 to 0.04 Gm. × Kg., just fatal. *Anesthetized Dog,* 1 to 3 mg. × Kg., quickening of heart, contraction of intestine, pressure variable. *Anesthetized Rabbit,* 2 mg. × Kg., vein, large vagus stimulation; 5 mg. × Kg., vein, peristalsis, Ex. (*). *Frog,* ordinary dose, 65 mg.; fatal dose, 100 mg. *Local,* Frog's heart, 0.1%, Ex. (*); Pupil, 1%, Ex. (*); Intestine, 1% (*).

Pilocarpus.—*Anesthetized Dog,* 0.15 to 1 Gm. × Kg., subcutaneous, acts like 1 to 3 mg. of Pilocarpin.

Piperidin.—*Dog,* 0.02 Gm. × Kg., subcutaneous, ordinary dose.

Platinum (calculated as metal).—Just fatal dose, mg. × Kg., subcutaneous: *Dog,* 7; *Rabbit,* 10; *Frog,* 125. *Rabbit,* 7 mg. of chlorid × Kg., subcutaneous, diuresis with albuminuria (the chlorid is neutralized with sodium carbonate, and diluted so that 1 c.c. = 5 mg.).

Potassium Chlorid.—*Rabbit,* 4 Gm. × Kg. (as 35%), subcutaneous, death in 30 minutes. *Anesthetized Mammal,* 1 c.c. × Kg. of 1%, vein, stops heart, Ex. (Myocardiogram) (*). *Frog,* 0.1 Gm., fatal (*). *Frog's Muscle,* 1%, paralysis in 30 to 50 minutes (*); after veratrin, $^1/_{100}$%, Ex. (*).

Psychotrin.—*Dog,* 10 mg. × Kg., subcutaneous, no effect. *Guinea Pig,* 20 to 30 mg. × Kg., subcutaneous, just fatal.

Pyridin.—*Rabbit,* 1.3 Gm. × Kg., subcutaneous, almost no effect; 2.6 Gm. × Kg., subcutaneous, convulsions, paralysis, death in 4½ hours. *Frog,* 0.1 Gm., subcutaneous, almost fatal.

Pyrocatechin.—*Dog,* 2 mg. × Kg., vein, slight rise of blood pressure; 8 mg., convulsive (*).

Pyrogallol.—*Dog,* 0.2 Gm. × Kg., subcutaneous, or 0.125 Gm. × Kg., stomach, fatal in two days.

Quinine Hydrochlorid.—*Man,* mouth, urine, 0.2 Gm., Ex. (*). *Mammals,* metabolism, 0.05 Gm. × Kg., Ex. *Anesthetized Dog,* 10 to 100 mg. × Kg., vein (ordinary dose, 10 mg. × Kg.), heart weaker and stops in three minutes before respiration, pressure falls at once (*). *Rabbit,* 0.5 Gm. × Kg., hydrobromid (hypodermic?), just fatal. *Pigeon,* 0.4 Gm. × Kg., hydrobromid, just fatal. *Frog,* 0.5 Gm. × Kg. hydrobromid or 0.4 Gm. × Kg. hydrochlorid, just fatal. *Frog's Muscle,* local, 1 : 10,000 to 1 : 100, Ex. (*). *Frog's Heart,* local, 1 : 50,000, slows and strengthens; 1 : 10,000, slows, weakens and stops, Ex. (*). *Frog,* 0.01 Gm., subcutaneous; stops emigration of leucocytes through mesentery; paralysis begins in ten minutes, and is complete in one hour (*); less than 1 : 1,000 interferes with *peptic digestion* (*); less than ½% with *oxydases* (*).

Rhubarb.—*Man,* 1 Gm., mouth, urine, Ex. (*). *Dog,* 5 Gm., stomach, purgative.

Ricin (Merck's).—*Rabbit,* 0.03 mg. × Kg., vein, or 0.07 mg. × Kg., subcutaneous, just fatal in 24 to 36 hours.

Salicylate of Sodium.—*Dog,* 0.2 Gm. × Kg., and *Rabbit,* 0.5 Gm. × Kg. (stomach?), fatal.

Salol.—*Man,* 0.3 Gm., mouth, urine, Ex. (*).

Sanguinaria (*).—Subcutaneous: *Guinea Pig,* to 1 Gm. × Kg., no effect; 10 Gm. × Kg., just fatal in six hours, paralytic. *White Rat,* 4 Gm. × Kg., just fatal in six or seven hours. *Frog,* 22 mg. × Gm., just fatal. *Frog's heart,* local, 1 : 25, no effect.

Santonin.—*Man,* mouth, urine, 0.03 Gm., Ex. (*) (Dissolved in NaOH, subcutaneous): *Dog,* 0.5 Gm. × Kg., convulsions, recovery. *Cat,* 1 Gm. × Kg., convulsions, fatal. *Rabbit,* 0.5 to 1 Gm. × Kg., stomach, convulsions in ½ hour, fall of temperature, recovery, Ex. (*); 2.5 Gm. × Kg., fatal.

Sapotoxin.—*Mammals,* vein, 1 to 2 mg. × Kg., fatal. *Cat,* subcu-

taneous, 10 to 30 mg. × Kg., ordinary dose; 40 mg. × Kg., fatal. *Local, Frog's* Muscle, 0.1%, Ex. (*). *Blood,* laking, Ex. (*).

SCILLA (*).—*Dog,* 0.1 Gm. × Kg., stomach, slowed heart; 2 Gm. × Kg., stomach, vomiting. *Guinea Pig,* 0.4 Gm. × Kg., subcutaneous, just fatal. *White Rat,* 20 Gm. × Kg., subcutaneous, just fatal. *Frog,* 0.9 mg. × Gm., subcutaneous, just fatal. *Local,* Frogs heart, 1 : 50, stops by digitalis action. *Anesthetized Dog,* subcutaneous, 0.001 Gm. × Kg., slows heart; 0.01 Gm. × Kg., heart first slowed, then quickened, stops in 30 minutes.

SCILLAIN.—*Dog,* 1 mg. × Kg., fatal.

SENEGA.—*Dog,* 5 Gm., stomach, emetic, Ex.

SILICATE OF SODIUM.—*Mammals,* just fatal, 1.5 to 2.0 Gm. × Kg., stomach, 0.07 to 0.3 Gm. × Kg., intravenous. *Frog,* just fatal, 0.025 to 0.1 Gm.

SILVER NITRATE.—*Rabbit,* 2 c.c of 2%, subcutaneous, fever of 1 to 1.5° C. in some hours; 20 mg. × Kg. of the chlorid, subcutaneous, albuminuria (dissolved in sodium hyposulphite, 1 c.c. = 5 mg.).

SOLANIN.—*Rabbit,* 0.1 Gm. × Kg., fatal.

SPARTEIN SULPHATE.—*Guinea Pig,* 0.1 Gm. × Kg., subcutaneous, just fatal; also *Fish, Frog, Pigeon, and Rabbit,* 0.1 to 0.15 Gm. × Kg., subcutaneous, just fatal. *Rabbit,* 0.04 to 0.06 Gm. × Kg., vein, just fatal. *Anethetized Dog,* 0.025 Gm., subcutaneous, ordinary dose.

STROPHANTHIN.—*Guinea Pig,* 0.3 mg. × Kg., subcutaneous, just fatal. *Frog's heart,* just stopped by 0.025 mg.

STROPHANTHUS (*).—Subcutaneous: *Rabbit,* 0.2 Gm., fatal in few minutes. *Guinea Pig,* 6.8 to 9.8 mg. × Kg., just fatal. *White Rat,* 20 Gm. × Kg., just fatal. *Frog,* 0.01 to 0.025 mg. × Gm., just fatal. *Anesthetized Dog,* 0.0015 Gm. × Kg., therapeutic stage of digitalis action; 0.05 Gm. × Kg., toxic stage of digitalis action: 0.15 Gm. × Kg., sudden death, Ex. *Frog's heart,* local, 1 : 50, stops heart in systole.

STRYCHNIN SULPHATE OR NITRATE.—

Man, 2 mg., mouth, no effect on tactile sensation (*).

JUST FATAL DOSES × Kg.: *Dog,* 0.75 mg., subcutaneous; 2.0 to 3.9, stomach; 2.0, rectum; 5.5 bladder. *Cat,* 0.75 mg., subcutaneous. *Fox,* 1 mg. *Hedgehog,* 1 to 2 mg. *Rabbit,* 4.233 mg., stomach; Ex. (*); 0.57 to 0.583 mg., hypodermic. (According to Gies and Meltzer, 0.45 mg. × Kg. of the nitrate is surely fatal to white rabbits, while gray rabbits require 0.5 mg. × Kg.) Ex. * 0.353 mg. in vein. *Guinea Pig,* 4.5 to 4.75 mg., subcutaneous (*), Ex. *Mouse,* 0.772 mg., subcutaneous. *Fowl,* 2 mg., subcutaneous. *Pigeon,* 1.67 mg. subcutaneous. *Frog,* 5.55 mg. (*) (ordinary dose, localization of action, 0.25 mg. per animal, Ex). *Ring-Adder,* 23.1 mg., subcutaneous; Antidote, Ex. (*).

JUST TETANIC DOSES × Kg.: *Dog,* 0.468 mg., stomach; 0.248, subcutaneous or rectal. *Rabbit,* 3.0 mg., stomach; 0.155 mg., vein; 0.4 mg., subcutaneous; 0.578, rectal. *Guinea Pig,* 10 to 15% less than the fatal (*). *Frog,* 1 to 1.5 mg. (*). *Toad,* 1.6 mg.

JUST CONVULSIVE DOSES (× Kg): *Dog,* 0.175 mg., stomach; 0.1 mg. to 0.24 mg., subcutaneous (*) or rectal. *Rabbit,* 0.29 mg. to 0.4 mg., subcutaneous; 0.57 mg., rectal. *Mouse,* 0.615 mg., subcutaneous. Pigeon, 0.5 mg., subcutaneous.

"SCHRECKHAFT" (× Kg): *Dog,* 0.07 mg., subcutaneous. *Rab*bit, 0.2 mg., subcutaneous. Pigeon, 0.5 mg., subcutaneous.

NO PERCEPTIBLE EFFECT (× Kg): *Dog,* 0.05 mg., subcutaneous or rectal. Rabbit, 0.2 mg., subcutaneous; 0.4 mg., rectal.

Anesthetized Dog, 0.07 mg. × Kg., subcutaneous, therapeutic dose, Ex. (*) (blood pressure); 0.40 mg. × Kg.. tetanic dose (same experiment); 0.04 mg. × Kg., vein, therapeutic dose, Ex. (*) (Myocardiogram). *Anesthetized Rabbit,* therapeutic dose, 0.2 mg. × Kg., respiration, Ex. (*). *Local,* Frog's heart, 0.1%, Ex. (*).

SULFOCYANID OF POTASSIUM.—*Pigeon,* 0.5 to 0.75 Gm. × Kg., subcutaneous, just fatal.

SULFOCYANID OF SODIUM.—*Dog,* 35 c.c. × Kg. of 1.2%, vein, no serious effects (*).

SULPHATE OF SODIUM.—*Dog,* 100 c.c. × Kg. of 4.6% crystals, vein, diuretic, no serious effects (*); ordinary dose, 50 c.c. × Kg. of 2% (dry), vein, blood pressure, Ex. (*).

SUPRARENAL GLAND.—*Mammals,* 10 c.c. × Kg. of 1%, dry, vein, blood pressure, Ex. (*); myocardiogram, Ex. (*).

TARTRATE OF SODIUM.—*Dog,* 0.92 Gm. × Kg., vein, just fatal.

TETRAMETHYLAMIN HYDROCHLORID.—Subcutaneous, fatal, × Kg.: *Rabbit,* 0.007 mg. *Guinea Pig and Mouse,* 0.02 mg. *Frog,* 0.07 mg.

THALLIUM SALTS.—*Dog,* 0.5 to 1 Gm., stomach, or 0.15 Gm., subcutaneous, fatal. *Rabbit,* 0.5 Gm., stomach, or 0.04 to 0.06 Gm., subcutaneous or vein, fatal.

THEBAIN NITRATE.—*Rabbit,* 5 mg. × Kg. to 14.4 mg. × Kg., vein, or 21.2 mg. × Kg., subcutaneous, just fatal. *Frog,* 0.75 mg. to 10 mg., convulsions.

THEOBROMIN-SODIUM SALICYLATE (Diuretin).—*Man,* 2 Gm., maximal diuretic. *Rabbit,* 0.5 to 1 Gm. × Kg., stomach, Ex. (*) (Antidote); 0.05 Gm. × Kg., vein, Ex. (*). *Dog,* 10 mg. × Kg., vein (no other effect).

THEOPHYLLIN (Theocin).—*Dog,* vein, 0.1 Gm. × Kg., just fatal. *Guinea Pig,* 0.2 Gm. × Kg., vein, just fatal

THORIUM NITRATE (*).—*Dog,* stomach, 25 c.c. of 5%; no effect. *Rabbit,* stomach, 1 Gm. × Kg., no effect.

THORIUM NITRATE IN SODIUM CITRATE (*).—1 Gm. × Kg., vein, *dog;* or subcutaneous, *rabbit,* not acutely fatal; nor with *frog,* subcutaneous, 0.02 Gm.

TOBACCO.—*Anesthetized Dog,* 0.10 Gm. about corresponds to 5 mg. nicotin.

TOLUYLENDIAMIN.—*Dog,* 0.04 Gm. × Kg. (as watery solution), subcutaneous, fatal, solution of red corpuscles.

TURPENTINE.—*Dog,* 8 to 30 Gm., stomach, gastro-enteritis, hematuria, death through paralysis of central nervous system; 15 drops, stomach, diuretic.

URANIUM (calculated as metal).—Just fatal dose, subcutaneous, mg. × Kg.: *Dog,* 1.66; *Cat and Rat,* 0.41; *Rabbit,* 0.83; *Goat,* 1.66; *Birds* 40 to 44.

UREA.—*Dog,* 35 c.c. × Kg. of 0.9% in isotonic NaCl, vein, no serious effect (*).

URETHANE (*).—*Rabbit,* rectum, 0.5 to 0.75 Gm. × Kg., anesthetic, Ex. (*); 0.6 Gm. × Kg., severe degeneration of hepatic cells; 0.75 to 1 Gm. × Kg., just fatal; stomach, 1.0 to 1.5 Gm. × Kg., anesthetic.

VALERIAN OIL.—*Rabbit,* 0.5 Gm. × Kg., subcutaneous, prevents convulsions from 0.4 Gm. × Kg. Ammonium Carbonate, subcutaneous, if this is given two hours after the valerian.

VANADIUM (Metavanadate of Sodium).—*Rabbit,* just fatal, 0.01 to 0.07 Gm. × Kg., vein, or 0.2 Gm. × Kg., stomach.

VERATRIN SULPHATE.—*Rabbit,* 2 mg. × Kg., subcutaneous, convulsions, Ex. (*); 1 c.c. of 1%, stomach, gastric corrosion, Ex. (*). *Anesthetized Rabbit,* 0.1 mg., vein, or 1 mg., subcutaneous, increases pulse rate and blood pressure; 10 mg., vein, paralyzes heart. *Frog,* 0.25 mg., subcutaneous, ordinary dose, Ex. (*); 1 mg., fatal. *Local,* Frog's heart, ½%, systolic stoppage (*); Muscle, ⅕%; typical veratrin curve (*).

VERATRUM VIRIDE (*).—*Guinea Pig,* 45 mg. × Kg., subcutaneous, just fatal. *Frog,* 0.65 mg. × Gm., subcutaneous, just fatal.

YOHIMBIN.—*Mammals,* 0.5 mg. × Kg., hypodermic, erection; 6.5 mg. × Kg., hypodermic, just fatal.

ZINC (Zinc-sodium pyrophosphate, or zinc valerianate).—Calculated as ZnO: *Frog,* 2 to 12 mg., complete muscular paralysis. *Rabbit,* 0.08 to 0.09 Gm., vein or subcutaneous, just fatal. *Dog,* 0.07 to 0.12 Gm., vein, just fatal.

ZINC SULPHATE.—*Dog,* 50 c.c. of 1%, stomach, emetic (*). *Rabbit,* 0.04 Gm. × Kg. (stomach?), fatal. *Frog,* 1 to 2 mg. × Gm., subcutaneous, fatal.

ZYGADENUS (dried).—*Rabbit,* 0.6 Gm. × Kg., subcutaneous, just fatal (*).

PART IV.

APPENDIX.

A.—LISTS FOR THE STUDY OF MATERIA MEDICA.

Introductory.—The materia-medica sections of the text consist largely of reference data, the greater part of which it is useless to memorize, and from which a judicious selection must be made. This is attempted in the following lists, which contain the names of the more important preparations, divided into convenient lessons to correspond with the text. The student should keep a separate note-book, ruled in columns as illustrated in the schema,[1] into which the names of the drugs and the relevant data are entered as they are studied. The preparation of these tables is probably the most efficient method of learning Materia Medica. The synonyms, origin, miscibility, dose, and remarks will be found in the text, where reference to the lessons is made; in only a few cases will it be necessary to consult the index. The appearance, odor, and taste should be studied directly from the specimen. It is highly desirable that the physician should be somewhat familiar with the physical characters of the principal drugs, if for no other reason than that it will give him some confidence, save him some embarrassment, and guarantee the proper dispensing of his prescriptions. This knowledge may be of vital importance for the prompt diagnosis of poisoning. Those drugs which may be readily recognized by their physical character are marked with an asterisk.

The Materia Medica Museum should contain the drugs mentioned in the following exercises. These may be duplicated for large classes. It will be found convenient to arrange the drugs according to the les-[2]

	WHITE LABELS:
Strong Poison! Do Not Taste.	**Identification.**
(Red Label)	(Red Print)
Poison! Taste Cautiously.	**Important.**
(Blue Label)	(Blue Print)
Practically Harmless.	**Unimportant.**
(Green Label)	(Black Print)

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[1] Page 962.

[2] Continued on page 963.

SCHEMA FOR THE TABULATION OF MATERIA MEDICA NOTES.

LATIN NAME AND SYNONYM (1).	AVERAGE DOSE (U.S.P.).		*Origin:* (2) BOTANIC NAME. PART USED. IMPORTANT CONSTITUENTS.	TOXICITY (3).	*Physical Characters:* APPEARANCE. ODOR. TASTE.	MISCIBILITY OR SOLUBILITY.		REMARKS.
	Metric.	U. S. System.				Water.	Alcohol.	

Explanatory.

(1) Synonyms or English Names need only be entered if they differ markedly from the Latin name.

(2) The origin need only be given for drugs or preparations derived from the organic kingdom.

(3) Toxicity.—This column, which is given in the lists, indicates whether the drug may be safely tasted: **(H)** stands for practically harmless; **(C)**, taste cautiously; **(D.n.t.)**, Do not taste.

* The drugs marked by an asterisk should be studied sothat unlabelled specimens can be identified.

The other specimens should be learned sufficiently, so that the student is able to decide whether or not an unlabelled sample *may* or may not be whatever is suggested. For instance, whether a white powder *may* be arsenic trioxid; whether a colorless fluid may be Tincture of Nux Vomica, etc.

sons. A card index is almost indispensable. It should give the case, shelf, and bottle number, and these should also be placed on the containers. The labels should give the name of the drug; whether it is for identification, important, or unimportant; and whether it may be tasted. Separate gummed slips, distinguished by colors, are very handy for this purpose (see page 961).

Other drugs — especially crude specimens — are valuable for reference, but may be dispensed with. Illustrations and herbarium specimens of important and domestic medicinal plants are also very profitable.

Latin Name.	Toxicity.	Remarks.
LESSON I.— DYES (Chapter VI, p. 102).		
Tr. Persionis	H	
Tr. Persionis Co.	H	2% Persionis. 10% Caramel.
Tr. Curcumæ	H	
Caramel	H	Partly carbonized sugar.
Liq. Carmini	C	With ammonia and ⅓ glycerin.
DEMULCENTS (page 755).		
*Acacia	H	
Mucilago Acaciæ	H	Strength.
Syr. Acaciæ	H	Strength.
SWEETENING AGENTS. (p. 104 and 105.)		
*Saccharum	H	
*Syrupus	H	85 Gm. in 100 c.c.
Benzosulphinidum	D.n.t.	Sweetening power.
*Glycerinum	H	
*Glycyrrhiza	H	Draw sketch.
*Pulv. Glycyrrhizæ	H	
*Fldext. Glycyrrhizæ	H	5% Ammonia water.
Ext. Glycyrrhizæ	H	
Syr. Glycyrrhizæ	H	
LESSON 2.— FLAVORS (CRUDE DRUGS) (Chapter VI, p. 106).		
*Lavandula	H	
*Anthemis	H	
*Vanilla	H	
*Mentha Piperita	H	Draw sketch.
*Carum	H	
*Anisum	H	
*Coriandrum	H	
*Sassafras	H	
*Caryophyllus	H	
*Cinnamomum	H	Sketch.
*Myristica	H	
*Macis	H	Sketch.
*Piper	H	"
*Cardamomum	H	

Latin Name.		
*Zingiber	H	Sketch.
*Capsicum	H	"
*Amygdala Amara	C	"
LESSON 3.—FLAVORS (PREPARATIONS) (Chapter VI, p. 110).		
*Oleum Caryophylli	C	
* " Cinnamomi	C	
* " Gaultheriæ	C	
* " Limonis	C	
* " Menthæ Pip.	C	
* " Menthæ Vir.	C	
*Aqua Cinnamomi	H	
* " Menthæ Pip.	H	
* " Rosæ	H	
*Spir. Gaultheriæ	C	
* " Menthæ Pip.	C	
*Elixir Aromatic	H	
" Adjuvans	H	Contains licorice.
*Tinct. Limonis Cort	C	
* " Tolutana	C	
* " Zingiberis	C	
LESSON 4.—FLAVORS (PREPARATIONS) (Chapter VI, p. 111).		
Tinct. Cinnamomi	C	
" Gentianæ Co.	C	
" Lavandulæ Co.	C	
" Vanillæ	C	
Syr. Ac. Citrici	H	
" Aurantii	H	
" Limonis	H	
" Picis Liq.	H	
" Pruni Virg.	H	
" Sarsapar. Co.	H	
" Tolutanus	H	
" Zingiberis	H	
" Glycyrrhizæ	H	
Species Pectorales	H	**Ingredients:**
LESSON 5.—SULPHUR COMPOUNDS (Chapter XXVIII, p. 675).		
*Sulphur Sublimatum	C	
Sulphur Lotum	C	
Unguentum Sulphuris	D.n.t.	
Pulvis Glycyrrhizæ Comp.	C	**Ingredients are:**
Sulphur Precipitatum	C	
Calx Sulphurata	C	
*Potassa Sulphurata	D.n.t.	
Sod. Thiosulphas	C	
*Ichthyol	C	

Latin Name.	Tox-icity.	Remarks.
Lesson 6.—Haloids (Chapter XXVIII, p. 679).		
Bromum	D.n.t.	*Do not smell.*
Liquor Chlori Compositus...	C	
*Calx Chlorinata	D.n.t.	
Liq. Sodæ Chloratæ..........	D.n.t.	
*Iodum	D.n.t.	
*Liq. Iodi Compositus........	C	
*Tr. Iodi	C	
*Iodoformum	D.n.t.	
Thymolis Iodidum	D.n.t.	
*Aq. Hydrogeni Dioxidi......	C	
Lesson 7.—Vegetable Astringents (Chapter XXVIII, p. 688).		
*Ac. Tannicum	C	
Ung. Ac. Tannici............	D.n.t.	Strength:
Glycer. Ac. Tannici.........	D.n.t.	"
Tannalbin	C	
Tinct. Gambir Co...........	C	
" Krameriæ	C	
" Kino	C	
Ext. Hæmatoxylon	C	
*Galla	C	
Sun Cholera Mixture........	C	Ingredients:
The principal incompatibilities of Tannins are:		

Lesson 8.—Astringents and Antiseptics (Chapter XXVIII, p. 692). Tabulate the proper strength for (1) Ulcers, Gargles, Rectal and Vaginal Injections; (2) Urethral Injections and Eye-waters:

Sodii Chloridum ....
Sodii Bicarbonas ....
Iodum ....
Zinci Sulphas ....
Zinci Phenolsulphonas ......
Hydrargyri Chloridum Corr..
Argenti Nitras ....
Argonin ....
Tr. Ferri Chloridi ....
Alumen ....

Cupri Sulphas ....
Ac. Tannicum ....
Plumbi Acetas ....
Potassii Permanganas ....
Phenol ....
Ac. Boricum ....
Cocaina ....
Hydrastinina ....
Atropinæ Sulph. ....
Physostigminæ Sulph. ......

Latin Name.		
Lesson 9.—Hysteric Sedatives (Chapter XXIX, p. 696).		
*Valeriana	C	
*Tr. Valerian. Ammon........	C	
Ammonii Valeras	C	

Latin Name.	Toxicity.	Remarks.
*Asafœtida	C	
*Tr. Asafœtidæ	C	
Pil. Asafœtidæ	D.n.t.	Strength:
RUBEFACIENT OILS (p. 697).		
*Ol. Terebinthinæ	C	Ingredients:
Liniment. Terebinth.	C	
Ol. Rosmarini	C	
*Arnica	C	
Tr. Arnicæ	C	Alcohol.
*Aq. Hamamelidis		
LESSON 10.—STIMULANTS FOR ULCERS (Chapter XXIX, p. 699).		
*Balsamum Peruvianum	C	
Myrrha	C	
Tr. Myrrhæ	C	
Benzoinum	C	
Tr. Benzoini Comp.	C	
URINARY DISINFECTANTS. (p. 700).		
*Copaiba	C	Ingredients:
Mist. Copaibæ Comp.	C	
*Cubeba	C	
Ol. Cubebæ	C	Draw sketch.
Tinct. Cubebæ	C	Strength of Trochisci Cubebæ.
Oleoresina Cubebæ	C	
*Ol. Santali	C	
Fldext. Matico	C	
LESSON 11.—DIURETIC OILS (Chapter XXIX, p. 701).		
*Juniperus	C	Draw sketch.
Spir. Juniperi Comp.	C	Ingredients:
*Buchu	C	Draw sketch.
Fldext. Buchu		
STIMULANTS TO BRONCHIAL MUCOSA AND RESPIRATORY ANTISEPTICS (p. 702).		
Terebenum	C	
Terpini Hydras	C	
Oleum Eucalypti	C	
Eucalyptol	C	
Balsamum Tolutanum	C	
*Syr. Tolutanus	C	(See Lesson 4).
Fldext. Grindeliæ	C	
LESSON 12.—TOXIC AND ECBOLIC VOLATILE OILS (Chapter XXIX, p. 703).		
*Ol. Sabinæ	D.n.t.	
*Tanacetum	D.n.t.	

Latin Name.	Toxicity.	Remarks.
*Oleum Rutæ	D.n.t.	
*Hedeoma	D.n.t.	
*Oleum Hedeomæ	D.n.t.	
Mustard Oil Group (p. 704).		
*Sinapis Alba	C	
*Sinapis Nigra	C	
*Spiritus Sinapis	D.n.t.	
Charta Sinapis	D.n.t.	
Thiosinamin	C	
Cantharidin Group (p. 707).		
*Cantharis	D.n.t.	Draw sketch.
Ceratum Cantharidis	D.n.t.	
Tr. Cantharidis	D.n.t.	Strength:
Capsicum	C	Strength:
Tr. Capsici	C	(See Lesson 2).
Chrysarobinum	D.n.t.	

Lesson 13.—Linaments (state ingredients) Chapter XXIX, p. 718).

Lin. Ammoniæ	D.n.t.	Lin. Saponis	D.n.t.
" Belladonnæ	D.n.t.	" Sinapis Comp.	D.n.t.
" Calcis	D.n t.	" Cantharidis	D.n.t.
" Camphoræ	D.n.t.	" Aconiti	D.n.t.
" Chloroformi	D.n.t.	" Sinapis	D.n.t.

Lesson 14.—Simple Bitters (Chapter XXX, p. 722).		
Tr. Calumbæ	C	
*Gentiana	C	
Tr. Gentianæ Comp.	C	(See Lesson 4).
Elixir Gentianæ	C	
*Quassia	C	
Tr. Quassiæ	C	
Elix. Taraxaci Comp.	C	
Astringent Bitters (p. 723).		
Tr. Serpentariæ	C	
Fldext. Cimicifugæ	C	
Aromatic Bitters (p. 724).		
*Calamus	C	
Tr. Aurantii Amari	C	
Aromatics, Carminatives and Condiments (p. 725).		
Spir. Menthæ Piperitæ		
Tinct. Zingiberis		
Tinct. Cardamomi Co.		
Pil. Asafœtidæ		Ingredients:

Latin Name.	Toxicity.	Remarks.
Lesson 15.—Cathartic Oils (Chapter XXX, p. 728).		
Ol. Tiglii	D.n.t.	
*Ol. Ricini	C	
Emodin Group (p. 729).		
*Senna	H	Draw sketch.
Fldext. Sennæ	C	Why previous exhaustion with alcohol?
Inf. Sennæ Co.	H	Ingredients:
Pulv. Glycyrrh. Co.	H	“
Species Laxantes	H	“
*Rheum	H	
Pulv. Rhei Co.	C	Ingredients:
Pil. Rhei Co.	D.n.t.	“
Tinct. Rhei Arom.	C	
Syr. Rhei Arom.	H	
Mist. Rhei et Sodæ.	H	Ingredients:
*Fldext. Rhamni Pursh.	C	Why should cascara be stored?
Fldext. Rhamni Pursh. Arom.	C	How is bitter taste lessened?
Aloe	C	Name official varieties.
*Tinct. Aloes	C	
Pil. Aloes		Ingredients:
“ “ et Ferri		“
“ “ et Myrrhæ		“
Pil. Laxativæ Co.		“
Lesson 16.—Anhydrid Cathartics (Chapter XXX, p. 733).		
Jalapa	D.n.t.	Draw sketch.
Pulvis Jalapæ Comp.	D.n.t.	Ingredients:
Resina Scammonii	D.n.t.	
Resina Podophylli	D.n.t.	
*Colocynthis	C	Draw sketch.
Ext. Colocynthydis Comp.	D.n.t.	Ingredients:
Pil. Catharticæ Comp.	D.n.t.	“
Pil. Catharticæ Vegetabilis.	D.n.t.	Ingredients:
Trituratio Elaterini	D.n.t.	
Cambogia	D.n.t.	
Manna	H	
Carbo. Ligni	H	
Suppos. Glycerini	D.n.t.	**Strength:**
Fel. Bovis Purific.	C	
Lesson 17.—Anthelmintics (Chapter XXX, p. 744).		
*Pepo	D.n.t.	
Aspidium	D.n.t.	
Oleoresina Aspidii	D.n.t.	
Pelletierinæ Tannas	D.n.t.	
Santoninum	D.n.t.	
Trochisci Santonini	D.n.t.	Strength:

Latin Name.	Tox-icity.	Remarks.
Lesson 18.—Strychnin Group (Chapter VIII, p. 160).		
*Nux Vomica	D.n.t.	Name per cent. of Strychnin in each preparation.
Tr. Nucis Vomicæ	C	Name alkaloids. Draw sketch.
Ext. Nucis Vomicæ	D.n.t.	
Strychninæ Sulphas	D.n.t.	Solubility in water:
Elixir Fer. Quin. et Strych. Phosph.	C	Ingredients in dose:
Caffein Group (p. 173).		
*Caffea	H	
*Thea	H	
Theobroma	H	
Caffeina Citrata	C	
Caffeina Citrata Effervescens.	H	
Theobrominæ-Sodio-Salicylas.	C	
Picrotoxin Group (p. 177).		
Picrotoxinum	D.n.t.	
Cocculus Indicus	D.n.t.	
Cicuta Virosa	D.n.t.	
Phytolaccæ Fructus	C.	

Lesson 19.— Morphin Group (Chapter IX, p. 202).

Name the principal alkaloids and acid of opium. State the opium and morphin percentage of each of the preparations.

*Opium	C	
Opii Pulvis	C	
Opium Deodoratum	C	How made? What purpose?
Pil. Opii		
*Tr. Opii	C	Dose for infants: Main Ingredients:
*Tr. Opii Camph.	C	
Pulv. Ipecac et Opii	C	Ingredients:
Tinct. Ipecac et Opii	C	"
Lotio Opii et Plumbi	D.n.t.	"
Morphinæ Hydrochlor.	D.n.t.	Solubility in water:
Morphinæ Sulphas	D.n.t.	" " "
Codeina	D.n.t.	
Codeinæ Phosphas	D.n.t.	
Heroinæ Hydrochlor.	D.n.t.	
Lesson 20.— Sundry Organic Narcotics (Chapter IX, p. 207).		
Ext. Cannabis Indicæ	C	
Tr. Cannabis Indicæ	C	
Lupulinum	C	
*Hydrastis	C	Principal Alkaloids: Draw sketch.
Tinct. Hydrastis	C	
Glyceritum Hydrastis	C	Strength:

Latin Name.	Tox-icity.	Remarks.
*Sanguinaria	C	Draw sketch.
Hydrastininæ Hydrochl	D.n.t.	
LESSON 21.—COCAIN GROUP (Chapter X, p. 222).		
Vinum Cocæ	C	
Cocainæ Hydrochlor.	D.n.t.	Solubility in water:
Eucain (beta)	D.n.t.	" " "
Orthoform	D.n.t.	" " "
Elixir Eriodictyon Co.	H	

LESSON 22.—ATROPIN GROUP (Chapter XI, p. 242).

The important alkaloids belonging to the group are:
The important drugs belonging to the group are:
The average per cent. of alkaloids is:
The ordinary dose of the Fluidextracts is:
The strength of the Tinctures is:
The strength of the Extracts is;
How does the strength and nature of the Hyoscaymus constituents differ from that of the other drugs?

Stramonium	D.n.t.	
Tinct. Bellad. Fol.	C	
Ext. Bellad. Fol.	D.n.t.	
Emplastrum Bellad.	D.n.t.	
Linim. Bellad.	D.n.t.	Ingredients:
Tinct. Hyoscyami	C	
Atropinæ Sulphas	D.n.t.	Sol. in water: Strength for use in eye:
Homatrop. Hydrobrom.	D.n.t.	Strength for use in eye:
Hyoscinæ Hydrobrom.	D.n.t.	Sol. in water: Synonym:
LESSON 23.—NICOTIN, PILOCARPIN, PHYSOSTIGMIN, ETC. (Chapter XII, p. 284).		
State the solubility of the alkaloids in water.		
Pilocarpin. Hydrochlor.	D.n.t.	
Curara	D.n.t.	Origin, constituents:
*Nicotina	D.n.t.	
Fluidextractum Conii	D.n.t.	
Coniina	D.n.t.	
Tinctura Gelsemii	D.n.t.	
Tinctura Lobeliæ	D.n.t.	
Scoparius	C	Important constituents:
Sparteinæ Sulphas	D.n.t.	
Physostigminæ Sulphas	D.n.t.	Synonym. Strength for eye:
LESSON 24.—INTERNAL SECRETIONS (Chapter XIII).		
Gland. Suprarenales Siccæ	D.n.t.	p. 295.
Suprarenal Alkaloid	D.n.t.	
Gland Thyroid. Siccæ	D.n.t.	p. 300.
Nuclein	D.n.t.	p. 301.

Latin Name.	Tox-icity.	Remarks.
LESSON 25.— EMETICS (Chapter XIV).		
State the emetic and nauseant doses.		
Apomorph. Hydrochlor.	D.n.t.	p. 307.
*Ipecacuanha	C	Draw sketch. p. 310.
Pulvis Ipecac.	C	
Syrupus Ipec.	C	
Vinum Ipec.	C	
Syr. Senegæ	C	p. 313.
Ammonii Carbonas	C	
Ant. et Pot. Tart.	D.n.t.	
Syr. Scillæ Co.	C	Ingredients:
*Cupri Sulphas	C	
LESSON 26.— ACONITE SERIES (Chapter XV).		
*Aconitum	D.n.t.	Draw sketch. p. 323.
Tinct. Aconiti	C	Strength:
Aconitina	D.n.t.	
Tinct. Veratri	C	Strength. p. 329.
Veratrina	D.n.t.	
Vin. Colchici Sem.	C	p. 330.
LESSON 27.— QUININ GROUP (Chapter XVI, p. 341).		
Cinchona	H	Principal alkaloids; per cent of alkaloids.
Tinct. Cinchonæ	C	
Tinct. Cinchon. Co.	C	Ingredients:
*Quininæ Sulph.	C	Solubility in water:
" Bisulph.	C	" " "
" Hydrochlor.	C	" " "
Euquinin	C	
LESSON 28.— ANTIPYRETICS (Chapter XVII, p. 354).		
Antipyrina	C	
*Acetanilidum	C	
Pulv. Acetanilidi Comp.	C	Composition.
Acetphenetidinum	C	
LESSON 29.— COAL-TAR ANTISEPTICS (Chapter XVII, p. 364).		
State the strength for local use.		
*Phenol	D.n.t.	%.
*Phenol Liquefactum	D.n.t.	%.
Ung. Phenolis	D.n.t.	
Phenylis Salicylas	C	
Cresol	D.n.t.	%.
Liq. Cresolis Comp.	D.n.t.	

Latin Name.	Toxicity.	Remarks.
Pyrogallol	D.n.t.	
Resorcinol	C	Draw sketch.
*Uva Ursi	H	
*Creosotum	C	
Guaiacol	C	
Guaiacoli Carbonas	C	
*Thymol	C	
Liq. Antisept.	C	Main ingredients:
LESSON 30.—COAL-TAR ANTISEPTICS, Continued (Chapter XVII, p. 371).		
Pix Liquida	D.n.t.	
*Syr. Picis Liq.	H	
Methylthioninæ Hydrochlor.	D.n.t.	
Acid. Picricum	D.n.t.	
Acid. Salicyl.	C	
*Sodii Salicyl.	C	
*Methylis Salicyl.	C	
Aspirin	C	
Acid. Benzoic.	C	
Sodii Benzoas	C	
Naphthalinum	C	
Betanaphthol	C	
Serum Antidiphther.	D.n.t.	

LESSON 31.—ALCOHOLIC LIQUIDS (Chapter XIX, p. 423).
State the alcoholic strength (by volume).

*Alcohol	C	Vinum Album
Alcohol Dilutum	C	" Rubrum
*Spir. Frumenti	C	" Xericum
*Spir. Vini Gall.	C	" Portense
Rum	C	Champagne
Gin	C	Ale and Porter
		Beer
LESSON 32.—ANESTHETICS (Chapter XIX, p. 442).		
*Chloroformum	C	%.
Spir. Chloroformi	C	
Bromoformum	C	
Ethylis Chloridum	D.n.t.	
*Æther	C	
Spir. Ætheris	C	%.
Spir. Ætheris Comp.	C	Ingredients:
*Æther Aceticus	C	
LESSON 33.—HYDROCARBON HYPNOTICS (Chapter XIX, p. 444). State the solubility in water.		
*Chloralum Hydratum	C	
Chloral formamidum	C	
Chloroform Acetone	C	
Æthylis Carbamas	C	

Latin Name.	Toxicity.	Remarks.
Hedonal	C	
Veronal	C	
Sulphonmethanum	C	
Sulphonethylmethanum	C	
Paraldehydum	C	
Amylene Hydrate	C	
LESSON 34.— FORMALDEHYD GROUP (Chapter XIX, p. 452).		
*Liquor Formaldehydi	D.n.t.	Strength:
Paraform	C	(Formaldehyd Tablets.)
Hexamethylenamina	C	
LESSON 35.— CAMPHOR GROUP (Chapter XXI, p. 465).		
*Camphora	C	
*Spiritus Camphoræ	C	%.
*Liniment. Camphoræ	C	Ingredients and percent.
Ac. Camphoric.	C	
*Menthol.	C	
LESSON 36.— CYANID GROUP (Chapter XXI, p. 470).		
*Ac. Hydrocyan. Dil.	D.n.t.	
*Potassii Cyanidum	D.n.t.	
*Syr. Pruni Virgin.	H	
*Amygdala Amara	C	Draw sketch.
*Spir. Amygd. Amaræ	C	
LESSON 37.— NITRITES (Chapter XXI, p. 476).		
*Amylis Nitris	D.n.t.	
*Spir. Æther. Nitros.	C	%.
Sodii Nitris	D.n.t.	
Spir. Glycerylis Nitratis.	D.n.t.	%.
Tabellæ Trinitrini	D.n.t.	Strength.
LESSON 38.— DIGITALIS GROUP (Chapter XXII, p. 496).		
State the drugs of the group. Name the active constituents of digitalis, and their solubility in alcohol and water.		
*Digitalis	C	
Tinctura Digitalis	C	%.
Infusum Digitalis	C	%.
Tinctura Strophanthi	C	%.
Scilla	C	
Tinct. Scillæ	C	%.
Syr. Scillæ Comp.	C	Ingredients:

Latin Name.	Toxicity.	Remarks.
LESSON 39.—ERGOT GROUP (Chapter XXIII, p. 509).		
Name the active ingredients of Ergot.		
*Ergota	C	Draw sketch.
*Fluidext. Ergotæ	C	
Ext. Ergotæ	C	
Gossypii Cortex	C	
Fluidextr. Viburni Prunifol..	C	
LESSON 40.—SAPOTOXIN GROUP (Chapter XXIII, p. 514).		
Quillaja	C	%.
Syrupus Senegæ	C	Ingredients:
Syr. Sarsap. Co.	H	
LESSON 41.—COUGH MIXTURES (Chapter XXIII, p. 519).		
State main ingredients of		
Mist. Glycyrrh. Co.		(See Lesson 38.)
Syr. Scillæ Co.		
Troch. Cubebæ		
Species Pectorales		
Syr. Pini Strobi Co.		
LESSON 42.—OSMOTIC ACTION (Chapter XXIV, p. 540).		
*Sodii Chloridum		
Urea		

CATHARTIC SALTS p. 545).

State the ordinary dose of all soluble cathartic salts.

*Magnesii Carbonas	H	Sodii Phosphas	H
" Oxidum	H	Sodii Sulphas	H
* " Sulphas	H	*Saccharum Lactis	H
Pot. Bitart.	H	Liquor Magnesii Citr.	H
*Pot. et Sod. Tart.	H	Liq. Sodii Phosph. Co	H

State the ingredients of the white and blue Seidlitz powders. Name the principal effervescing cathartic salts and their dose.

LESSON 43.—CATHIONS (Chapter XXV, p. 558).		
Lithii Carbonas	C	
Lithii Citras Effervescens	C	
*Ammonii Carbonas	C	
*Spir. Ammoniæ Arom.	C	Ingredients:
Ammonii Chloridum	C	Strength of Troches:
Liq. Ammonii Acetatis	H	Should be freshly made, because:
*Creta Preparata	H	
Calcii Carbonas Precip.	H	
*Liquor Calcis	C	
Syrupus Calcis	C	
Calcii Phosphas Prec.	H	

Latin Name.	Toxicity.	Remarks.
Calcii Chloridum	C	
Barii Chloridum	D.n.t.	Antidote:
Strontii Lactas	C	
LESSON 44.—ANIONS (Chapter XXV, p. 568).		
Potassii Bromidum	C	The general solubility and dose of all bromids is:
“ Iodidum	C	The general dose and solubility of all iodids is:
“ Nitras	C	
* “ Chloras	C	Strength of Trochisci:
* “ Permanganas	D.n.t.	
“ Acetas	C	
“ Citras	C	
Acidum Oxalicum	D.n.t.	Antidote:
“ Boricum	C	Strength for local use:
“ Boricum Pulv.	C	“ “ “ “
Sodii Boras	C	“ “ “ “
Glyceritum Boroglycerini	D.n.t.	Percentage:

LESSON 45.—ACIDS
Chapter XXVI, p. 586).
The strength of all Dilute Acids is *æ*%; with what exceptions?

Acidum Hydrochloricum.....	D.n.t.	Ac. Sulphuricum Dil	D.n.t.
Acidum Hydrochloricum Dil.	C	*Ac. Aceticum Dilutum	C
Ac. Nitrohydrochloricum, Dil.	C	*Ac. Citricum	C
Ac. Nitricum	D.n.t.	*Syr. Ac. Citrici.....	C
Ac. Phosphoricum	D.n.t.	Ac. Oleicum	C
Ac. Phosphoricum Dil.......	C	Ac. Sulphurosum ...	C
Ac. Sulphuricum	D.n.t.	Ac. Trichloraceticum	C

LESSON 46.—ALKALIES (Chapter XXVI, p. 597).

The following are studied in preceding lessons: Magnesia and Magn. Carb.; Lip. and Syr. Calcis; Creta and Calc. Carb.; Sp. Ammon. Arom. and Amm. Carb.; Pot. Acetas, and Citras; Sod. Boras.

Soda	C	Potassii Carbonas ...	C
*Potassa	C	*Sodii Carbonas	C
Calx	C	*Sodii Bicarbonas	C
Liq. Potassæ Strength.......	C	Piperazin	C
Aq. Ammoniæ Strength.....	D.n.t.	Sapo	C

Name the main ingredients of Carlsbad and Hunyadi Waters.

LESSON 47.—METALS (Chapter XXVII).

LESSON 47.—METALS (Chapter XXVII). ARSENIC (p. 616).		All fluid arsenic preparations contain —% of arsenic. Their dose is— —
Arseni Trioxidum...........	D.n.t.	
Liq. Potassii Arsenitis........	D.n.t.	
Liq. Arseni et Hydrargyri Iodidi	D.n.t.	
Sod. Cacodylate	D.n.t.	

Latin Name.	Tox-icity.	Remarks.
ANTIMONY (p. 619).		
Antimonii et Potassii Tartras.	D.n.t.	
Vinum Antimonii	C	Contains Tartar Emetic —%.
Syr. Scillæ Comp............	C	Contains Tartar Emetic —%.
BISMUTH (p. 621).		
Bismuthi Subcarbonas	C	
*Bismuthi Subnitras	C	
Bismuthi Subgallas	C	
LESSON 48.—IRON (Chapter XXVII, p. 628).		
Liquor Ferri Subsulph......	C	
Ferrum Reductum	H	
Massa Ferri Carb............	D.n.t.	
Pil. Ferri Carb..............	D.n.t.	
Ferri Sulph. Exsicc..........	C	
Pil. Aloes et Ferri...........	D.n.t.	Ingredients:
Ferri et Amm. Tart..........	C	
Syr. Ferri Iodidi............	C	
*Tinct. Ferri Chlor...........	C	%.
Organic Iron Preparations...	C	
MANGANESE AND CHROMIUM. (p. 632).		
Mang. Diox. Præc...........	C	
*Pot. Permang...............	D.n.t.	
Chromii Trioxid.............	D.n.t.	
*Pot. Dichromas..............	D.n.t.	
LESSON 49.—ALUMINUM GROUP (Chapter XXVII, p. 633).		
Alumen	C	
SILVER GROUP (p. 636).		
Argenti Nitras	D.n.t.	Strength for local:
*Argenti Nitras Fusus........	D.n.t.	
Collargol	D.n.t.	
Organic Silver Prep........	D.n.t.	Strength for local:
Auri et Sod. Chlor.........	D.n.t.	%.
COPPER-ZINC GROUP (p. 638).		
State strength for local use.		
*Cupri Sulphas	D.n.t.	
Zinci Phenolsulph...........	D.n.t.	
Zinci Sulph................	C	
Liq. Zinci Chlor.............	D.n.t.	Strength:
Zinci Oxidum	C	
Ung. Zinci Oxidi...........	D.n.t.	%.
LESSON 50.—MERCURY (p. 645).		
State strength for local use.		
Massa Hydrargyri	D.n.t.	%.
*Ung. Hydrargyri	D.n.t.	%.
Ung. Hydrargyri Dilut.......	D.n.t.	%.

Latin Name.	Tox-icity.	Remarks.
ANTIMONY (p. 619).		
Hydrarg. Chlor. Mite	D.n.t.	
Hydrarg. Iodid. Flav	D.n.t.	
Lotio Nigra	D.n.t.	Ingredients:
Ung. Hydrarg. Ox. Rubr	D.n.t.	%.
Hydrarg. Chlor. Corros	D.n.t.	
Lotio Flava	D.n.t.	Ingredients:
Liq. Hydrarg. et Ars. Iod	D.n.t.	%.
Ung. Hydrarg. Nitratis	D.n.t.	

Give the Latin name of Gray Powder; White Precipitate.

Latin Name.	Tox-icity.	Remarks.
Lesson 51.—Lead (Chapter XXVII, p. 653).		
Plumbi Acetas	D.n.t.	
Liq. Plumbi Subacet	D.n.t.	%.
Liq. Plumbi Subacet. Dil	D.n.t.	%.
Emplastr. Plumbi	D.n.t.	
PHOSPHORUS (p. 658).		
*Phophorus	D.n.t.	Best solvent:
Pil. Phosphori	D.n.t.	Strength:
Dose of hypophosphites:		
Syr. Hypophosphitum	C	
Syr. Hypophosphitum cum Ferro	C	Strychnin in 8 c.c.:
Lesson 52.—Emollients (Chapter XXXI, p. 750).		
FLUID:		
Ol. Olivæ	H	
*Ol. Gossypii Seminis	H	
Ol. Lini	H	
Ac. Oleicum	C	
*Glycerinum	H	
*Petrolatum Liquidum	H	
SEMI-SOLID:		
*Ol. Theobromatis	H	
*Adeps Benzoinatus	H	
Adeps Lanæ Hydros	D.n.t.	
*Petrolatum	H	
*Petrolatum Album	H	
Unguentum	D.n.t.	Ingredients:
*Ung. Aquæ Rosæ	D.n.t.	Ingredients:
Ceratum	D.n.t.	Ingredients:
Lesson 53.—Waxes and Resins (Chapter XXXI, p. 752).		PLASTER-MASSES (p. 753). State the English name and the ingredients of the following Emplastra: Adhesivum, Belladonnæ, Capsici, Hydrargyri, Ichthyocollæ, Plumbi, Resinæ.
*Cera Flava	H	
*Cera Alba	H	
*Paraffinum	H	
*Resina	H	
Elastica	D.n.t.	
Gutta Percha	D.n.t.	

Latin Name.	Toxicity.	Remarks.
LESSON 54.—DEMULCENTS (Chapter XXXI, p. 754).		
*Linum	H	Draw sketch.
*Linum Contusum	H	
Cataplasma Kaolini	D.n.t.	Ingredients:
*Acacia	H	
*Mucilago Acaciæ	H	%.
*Tragacantha	H	Draw sketch.
*Cetraria	H	Draw sketch.
*Chondrus	H	Draw sketch.
*Gelatinum	H	
MECHANICAL PROTECTIVES:		
*Lycopodium	D.n.t.	
*Talcum	D.n.t.	
*Amylum	H	
*Collodium	D.n.t.	%.
Collodium Flexile	D.n.t.	Ingredients:
Gossypium Purif.	D.n.t.	
Calcii Sulphas Exsic.	D.n.t.	
Liq. Sodii Silicates	D.n.t.	
LESSON 55.—NUTRIENTS AND FERMENTS (Chapter XXXII, p. 757).		
Pepsinum	D.n.t.	Digestive Power:
Pepsinum Saccharatum	H	%.
Liquor Pepsini	H	
Glyceritum Pepsini	H	
Pancreatinum	D.n.t.	Digestive Power:
Papain	D.n.t.	
*Extr. Malti	H	
*Extr. Carnis	C	
Vin. Carnis et Ferri	C	
*Ol. Morrhuæ	H	
*Emuls. Ol. Morrhue	H	%.
Emuls. Ol. Morrhue cum Hypophos.	H	%.
Tinct. Guaiaci	C	

B.—BIBLIOGRAPHIC REFERENCES FOR COLLATERAL READING.

Introductory.— It is highly desirable that the student's knowledge of pharmacology should not be limited by the statements and views contained in a single text-book. Some excursions into the original literature are especialy valuable, and indeed indispensable, for a real understanding of the subject. Even elementary students should read and abstract at least a few of the papers in the subjoined lists, which may serve as a guide for this collateral reading. Advanced students and beginning investigators should aim to cover as many as possible of List IV. The lists have been compiled with a view to making them representative rather than exhaustive. Preference has been given to the papers which deal with general problems, or which illustrate methods of research, over those which deal with more circumscribed topics. Some of the latter have, however, been introduced, when they cover points of special interest. The more recent articles have usually been preferred, since they give a more representative view of the present standpoint of knowledge. They are also more useful as guides to the special literature of the subject. A number of older papers of classical value have, however, been retained. These should only be read in connection with the more recent papers, or under the critical guidance of the instructor. Indeed, the value of the entire course of reading may be manifolded by discussing the abstracts in seminars.

The accessibility of the papers has also been a factor in their selection.

These lists make no pretense to a complete bibliography of any subject. Those in search for further information may be guided by the references in the papers of List IV; by the more extensive bibliographies in some of the other text-books of List I (notably Binz, Cushny, Kobert, Schmiedeberg, Hale White, and Wood); in the critical bibliographies, especially of the Ergebnisse der Physiologie, and of the Biochemisches Centralblatt (the most important being quoted in List II); or by the references in the text. Only the name and year of publication are given in the latter; the exact reference can be found in the Bibliographic Register, preceding the Index.

List I. Reference Books — Systematic Pharmacology and Therapeutics:

The books marked * seem the most indispensable.

*1891. *Binz:* Vorlesungen ueber Pharmakologie. Berlin.
*1885. *Lauder Brunton:* Pharmacology, Therapeutics and Materia Medica. Philadelphia.
1898. *Lauder Brunton:* Lectures on the Actions of Medicines. New York.
1853–1856. *Buchheim:* Arzneimittellehre. Leipzig.
*1903. *Cushny:* Pharmacology and Therapeutics. Philadelphia.
*1904. *Heinz:* Handb. d. Path. und Pharmakol. Jena.
*1897. *Kobert:* Pharmakotherapie. Stuttgart.
1901. *Pembrey and Phillips:* Physiol. Action of Drugs. London.
1900. *Penzoldt:* Klinische Arzneibehandlung. Jena.
*1902. *Schmiedeberg:* Pharmakologie. Leipzig.
1901. *Tappeiner:* Arzneimittellehre. Leipzig.
*1901. *Hale White* (Editor): Textbook of Pharmacology and Therapeutics. Edinburgh.
*1902. *Wood:* Therapeutics. Philadelphia.
1904. *Yeo:* Manual of Medical Treatment. Chicago.

Pharmacognosy, Materia Medica, etc.

Bastin: Laboratory Exercises in Botany.
Coblentz: Handbook of Pharmacy. Philadelphia.
1882. *Draggendorff:* Pflanzenanalyse. Göttingen.
1898. *Draggendorff:* Heilpflanzen. Stuttgart.
1885. *Flückiger and Tschirch:* Pharmakognosie. Berlin.
Flückiger and Hanbury: Pharmacographia.
Gray's Manual of Botany.
*1900. *Hager:* Pharmaceutische Praxis (2 vol.). Berlin.
*1904. *Hatcher and Sollmann:* Textbook of Materia Medica. Saunders.
1882. *Husemann and Hilger:* Pflanzenstoffe (2 vol.).
Maisch: Organic Materia Medica. Philadelphia.
* *Mann:* Manual of Prescription Writing. New York.
* *National Dispensatory.*
National Formulary.

Remington: Practice of Pharmacy.
Robinson: Latin Grammar of Pharm. and Med. Philadelphia.
1901. *Roscoe and Schorlemmer's* Lehrb. d. Organ. Chemic. VI. Braunschreig.
United States Dispensatory.
*1905. *United States Pharmacopœia.*

General Toxicology:

* *Blyth:* Poisons: Their Effects and Detection.
1880. *Boehm, Naunyn and v. Boeck:* Handb. d. Vergiftungen.
* *Draggendorff:* Toxicologie.
1874. *Hermann:* Experimentelle Toxicologie. Berlin.
* *v. Hofman:* Atlas of Legal Medicine. Saunders.
1897. *v. Jasksch:* Die Vergiftungen.
*1901. *Kionka:* Grundriss d. Toxicologie. Leipzig.
*1904. *Kobert:* Lehrbuch der Intoxicationen. Stuttgart.
1901. *Kunkel:* Handbuch der Toxicologie. Jena.
1897. *Lewin:* Toxicologie. Wien.
*1852. *Orfila:* Traité des Poisons. Paris.
1903. *Peterson and Haines:* Legal Medicine and Toxicology.
Tanner: Memoranda of Poisons. Philadelphia.

Toxicologic Analysis: (See also Toxicology.)

1893. *Flückiger:* Reactions. Detroit.
1897. *Kippenberger:* Nachweis v. Giftstoffen. Berlin.
*1896. *Otto:* Ausmittlung der Gifte. Braunschweig.
*1897. *Schaer and Zenetti:* Anal. Chem. Uebungsarb. Berlin.
Holland, Medical Chemistry.
1885. *Wormley:* Microchemistry of Poisons.

List II. Larger Monographs:

1904. *Abderhalden:* Bibliographie des Alkohols. Berlin.
*1898. *Atwater and Langworthy:* Digest of Metabolism Experiments. Office Exp. St. Bulletin 45. U. S. Dept. Agr.
1887. *Erlenmeyer:* Morphiumsucht. Berlin.
*1901. *Fraenkel:* Arzneimittel-Synthese. Berlin.
*1900. *v. Fuerth:* Vergl. Chem. Physiol. d. niederen These. Jena.
*1902-1904. *Hamburger:* Osm. Druck und Ionenlehre. 3 vol. Wiesbaden.
1904. *Lewin:* Fruchtabtreibung d. Gifte. Berlin.
*1883. *Lewin:* Untoward Effects of Drugs. Detroit.
*1901. *Overton:* Studien üb. die Narkose. Jena.
1904. *Wassermann:* Immune Sera. J. Wiley & Sons.

List III. Journals and Abbreviations:

A. f. H.—Archiv für Hygiene.
Am. J. Ph.—American Journal of Physiology.
Am. J. Phar.—American Journal of Pharmacy.
Arch. de Phys.—Archives de Physiologie.
Arch. f. Phys.—Archiv für (Anatomie und) Physiologie.
Arch. int. Pharm. (A. i. P. T.)—Archiv international de Pharmacodynamie et Therapie.
Arch. it.—Archives italiannes de Biologie.
B. C.—Biochemisches Centralblatt.
Dorp. Arb.—Arbeiten aus den pharmakoligischen Institut. Dorput.
Du B.—Du Bois' Archiv für Physiologie.
Erg.—Asher & Spiro, Ergebnisse der Physiologie.
H. B.—Hofmeister's Beiträge. z. Chem. Phys. u. Path.
H.-S.—Hoppe-Seyler's Zeitschrift f. Physiol. Chemie.

J. A. M. A.—Journal American Medical Association.
J. de Ph.—Journal de Physiologie.
J. Exp. Med.—Journal of Experimental Medicine.
J. H. H. Bull.—Johns Hopkins Hospital Bulletin.
J. Med. Res.—Journal of Medical Research.
J. Ph.—(English) Journal of Physiology.
Pf.—Pflüger's Archiv f. d. gesamente Physiologie.
Schm.—Schmiedeberg's Arch. für exp. Path. und Pharmak.
Sk.—Skandinavisches Archiv für Physiologie.
Virch.—Virchow's Archiv für Path. Anat. u. Physiol.
Z. B.—Kühne's Zeitschrift für Biologie.

List IV. Selected Papers.

Arranged by the chapters of the book.

Methods of Instruction:
1890. Abel, J. J. Phil. Med. Journ., Sept. 1.
1902. Sollmann, T. J. A. M. A., Sept. 6.
1904. Sollmann, T. J. A. M. A., 43:452.

Assaying (Chapter IV):
1897. Keller. Inaug. Diss. Zurich.

Toxicology (Chapter V):
1902. Sollmann. Coffee and Tea as Antidotes. J. Med. Res., 7:43.
1904. Sollmann. Antagonism. Am. J. Phys., 10:352.
1905. Heffter (Excretion of organic substances). Erg. IV. J. 1:184 (Crit. Bibl.).

Strychnin (Chapter VIII):
1900. Baglioni. Arch. f. Phys. Suppl., :152.
1903. Gies and Meltzer. Am. J. Ph., 9:1.
1895. Gumprecht (Tetanus and older literature). Pf. 59:131.

Caffein (Chapter VIII):
Diuresis:
1886 & 1887. v. Schroeder. Schm., 22:39; (24:85).
1887. Phillips and Bradford. J. Ph., 8:117.
1894. Raphael. Dorp. Arb., 10:81.
1895. v. Sobieranski. Schm., 35:144.
1901. Anten. Arch. int. Phar., 8:455.
1901. Impens (Agurin). *Ib.*, 9:1.
Heart:
1901. Cushny and Naten. *Ib.*, 9:169.
Muscular Work:
1899. Schumburg. Arch. f. Phys. Suppl., :289.

Picrotoxin (Chapter VIII):
1899. Guinard and Dumarest. Arch. int. Phar., 6:283 and 403.

Morphin (Chapter IX):
1900. Faust (Habituation). Schm., 44:217.
1899. Impens (Heroin, etc.). Pf., 78:527.
1901. Bashford (Atropin antagonism). Arch. int. Phar., 8:311.
1901. Reichert. (Atropin antagonism). Ther. Monthly, May.
1903. Schneiderlin (Morphin-Scopolamin Anesthesia). Münch. Med. Woch., March 3.
1903. Jacquet (Gaseous Metabolism). Crit. Bibl. Erg., II J., 1:457.
1899. Dixon (Anhalonium). J. Ph., 25:69.
De Quincy. The Confessions of an Opium Eater.

Cocain (Chapter X).
1880. v. Anrep. Pf., 21:38.
1904. Dixon. J. Ph., 32:87.
1900. Bier (Spinal). Muench. Med. Woch., Nov. 21.
1903. Loewy and Mueller (Yohimbin). *Ib.*, No. 15.

Atropin, etc. (Chapters XI and XII):

General:

1898. Schulz (Eye). Arch. f. Phys., : 53.
1901. Bayliss and Starling (Intestine). J. Ph., 26: 125.
1905. Magnus (Intestine). Pf., 108: 1.
1905. Ott (Intestine). J. A. M. A., 44: 1919.
1903. Cannon (Intestine). *Ib.,* 40: 749.
1903. Dixon and Brodie (Bronchial Muscle). J. Ph., 19: 97.
1903. Dixon and Brodie (Pathol. Asthma). Trans. Path. Soc., : 54.
1900. Mathews, A. P. (Atropin, Saliva). Am. J. Ph., 4: 482.
1899. Lewin (Atropin, Resistance). Deut. Med. Woch., 25: 37.
1903 Cushny (Atropin and Hyoscyamin). J. Ph., 30: 176.
1900. Jowett and Marshall (Pilocarpin). Brit. Med. J., Oct.
1850. Cl. Bernard (Curare). Compt. Rend., 31: 533.
1856. Cl. Bernard (Curare). *Ib.,* 43: 825.
1894. Boehm (Curare). Schm., 35: 16.
1901. Rothberger (Curare). Pf., 87: 117.
1893. Cushny (Gelsemin). Schm., 31: 49.
1895. Cushny and Matthews (Spartein). *Ib.,* 35: 129.
1869. Schmiedeberg and Koppe (Muscarin). Leipzig.
1901. Carter (Poisonous Mushrooms). Am. J. Ph., 5: 138.
1890. Langley (Nicotin). J. Ph. 11: 123 (11: 509).
1890. Langley and Dickinson (Nicotin literature). J. Ph., 11: 265.
1901. Habermann (Tobacco-smoke). H.-S., 33: 55.
1864. Fraser (Physostigmin). Edinb. Med. J., 9: 36.
1876. Harnack and Witkowski (Physostigmin). Schm., 5: 401.
1903. Dixon (Apocodein). J. Ph., 30: 97.

Heart:

1898. Hedbom. Sk., 9: 1.
1895. Langendorff. Pf., 61: 292.
1898. Bock. Schm., 41: 158.
1899. Cleghorn. Am. J. Ph., 2: 273.
1893. Pickering (Embryonal Chick). J. Ph., 14: 383.

Vessels:

1894. Bradford and Dean. J. Ph., 16: 34.
1896. Paldrock. Dorp. Arb., 13: 1.
1899. Pick. Schm., 42: 426.

Suprarenal (Chapter XII):

1895. Oliver and Schaefer. J. Ph., 18: 230.
1901. Langley. J. Ph., 27: 237.
1901. Takamine. Am. J. Phar., 63: 523.
1904. Brodie and Dixon. J. Ph., 30: 476.
1905. Meltzer and Auer. J. Exp. Med., 7: 1.
1905. Elliott. J. Ph. 32: 401.

Thyroid (Chapter XII):

1903. Oswald (Critical Bibliography). B. C., 1: 249.

Phlorrhizin (Chapter XII):

1903. Pavy, Brodie and Sian. J. Ph., 29: 467.

Emetics (Chapter XIV):

1886. Schütz (Excised Stomach). Schm., 21: 341.
1903. Magnus (Crit. Bibl.). Erg., II J., 1: 637.
1874. Harnack (Apomorphin). Schm., 2: 254.
1901. Paul and Cownley. Am. J. Phar., 73.
1902. Lowin. Arch. int. Pharm., 11: 9.

Aconite, etc. (Chapter XV):

1897. S. A. Matthews (Aconite). J. Exp. Med., 2: 593.
1901. Bottazzi (Veratrin). Arch. J. Phys., : 377.
1890. Jacobj (Colchicum). Schm., 27: 110.

Quinin (Chapter XVI):
1868. Binz: Wesen der Chinin wirkung. Berlin.
1873, 1876, 1877. Binz. Schm., 1:18; 5:39; 7:275.
Coal Tar Derivatives (Chapter XVII):
1904. Loewi (Crit. Bibl. Temperature). Erg., III J., 1:332.
1890. Gottlieb (Antipyr. Action). Schm., 26:419.
1900. Baglioni (Carbolic Convulsion). Arch. f. Phys. Suppl., :193.
1899. Dreser (Aspirin). Pf., 76:306.
1897. Benedicenti (Methemoglobin). Arch. f. Phys., :210.
Toxins and Antitoxins (Chapter XVIII):
(See Reference Books.)
Washbourn. Article on Serum-Therapy in White's Textbook, pp. 770 to 817.
v. Fuerth. Poisons of invertebrates in Vergl. Chem., pp. 304 to 368.
1905. Michaelis (Crit. Bibl. Precipitins). B. C., 3:693.
1903. Meyer and Ransom (Tetanus Toxin). Schm., 49:369.
1899. Rolly (Diphtheria Toxin on Heart). Schm., 42:283.
Hydrocarbon Narcotics (Chapter XIX):
General:
1901. Overton. Studien über die Narkose. Jena.
1899. Meyer. Schm., 42:109; 46:338.
1904. Abderhalden. Bibliographie üb. d. Alkohol. Berlin. (504 p.) Classified Titles:
1904. Sollmann (Critical Bibliography Anesthetics). Am. Med., 8:455.
Alcohol:
1887. Bunge. Die Alkoholfrage. Leipzig.
1898. Baer (Relative Toxicity). Arch. f. Phys., :287.
1902. Hunt (Methyl Alcohol). J. H. H. Bull., 13:213.
1898. Chittenden, Mendel and Jackson (on Digestion). Am. J. Ph., 1:164.
1903. Rosemann (Food-value). Pf., 100:348.
1892. Kraepelin. Ueb. d. Beerinfl. einiger psych. Vorgänge d. einige Arzneimittel. Jena.
1899. Wendelstadt (Respiration). Pf., 76:223.
1904. Hellsten (Muscular Work). Sk., 16:139.
Anesthetics:
1875. Cl. Bernard. Leçons sur les Anesthetiques. Paris.
1891. Report of the Hyderabad Commission. Bombay.
1903. Report of Chloroform Commission. Suppl. Brit. Med. J.
1894. Spenzer (Dosage of Ether). Schm., 33:407.
1895. Rosenfeld (Dosage of Chloroform). *Ib.*, 37:54.
1890. Dastre. Les Anesthetiques. Paris.
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1903. Hill and Macleod (Atmosph. Pressure). J. Hyg., 3:401.
1900. Haldane (CO). J. Ph., 25:225.
1903. Vahlen (Illum. Gas). Schm., 49:245.
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1897. Cushny. J. Exp. Med., 2: 233.
1899. Cushny. J. Ph., 25: 49.
1901. Gottlieb and Magnus. Schm., 47: 135.
1903. Gottlieb and Magnus. *Ib.*, 51: 30.
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1884. Kobert. Schm., 18: 316.
1891, '92 & '95. Grünfeld. Dorp. Arb., 7: 108; 8: 115; 12: 205.
1897. Jacobj. Schm., 39: 85.
1905. Sollmann and Brown. J. A. M. A., 45: July 22.
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1905. Bass. Centbl. f. Grenzgeb. d. Med. Chir. 7, Nos. 21 and 22.
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1887. Kobert. Schm., 23: 233.
1904. Kobert. Saponinsubstanzen. Stuttgart. (112 p.)
1899. Stewart, G. N. J. Ph., 24: 211.
1902. Stewart, G. N. J. Exp. Med., 6: 257.
1901. Ransom. Deut. Med. Woch., : 194.
Salt Actions (Chapters XXIV and XXV):
1902–1904. Hamburger. (See Reference Books).
1905. Aron. Colloid solutions (Crit. Bibl.) B. C. 3: 461, 501; 4: 505, 553.
1873. Bunge. Z. B., 9: 104.
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1896. Bosc and Vedel (Massive Injections). Arch. de Phys., 8: 937.
1898. Wallace and Cushny. Am. J. Ph., 1: 411.
1898. Münzer. Schm., 41: 74.
1899. Straub. G. B., 38: 537.
1900. Magnus. Schm., 44: 68.
1901. Sollmann. Schm., 46: 1.
1902. Cushny. J. P., 27: 429; 28: 431.
1903 & 1905. Sollmann. Am. J. Ph., 9: 425; 13: 241-303.
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General:
1873. Forster (Chlorid Excretion). Z. B., 9: 279.
1898. Howell (Heart). Am. J. Ph., 2: 47.
1901. Locke (Solution). Cbl. Ph., 14: 620.
1902. Loeb, J. Am. J. Ph., 6: 410.
1903. McCallum, J. B. (Peristalsis). Calif. Physiol., 1: 115.
1903. Widal and Javal (Cl. Retention). Presse Med., No. 51.
1903. Pauli. Münch. Med. Woch., No. 4.
1903. Heffter (Crit. Bibl. Excretion). Erg., II J., 1: 95.
1903. Höber (Crit. Bibl. Colloids). B. C., 1: 497.
1903. Matthews (Diuretic Solution). J. A. M. A., 41: 566 and 616.
1904. Mathews, A. P. (Solution Tension). Am. J. Ph., 11: 455.
1905. Mathews, A. P. (Antitoxic Action). *Ib.*, 12: 419.
1905. Macallum, A. B. (K. in cells). J. Ph., 32: 95.
1903. Tappeiner and Jesionek (Fluorescence). Münch. Med. Woch., No. 47.
1905. Michaelis (Fluorescence, Crit. Bibl.) B. C. 4: 173.
Specific Ions:
1886 & 1887. Marchand (Chlorates). Schm., 22: 201; 23: 273.
1900. Formánek (Ammonium). Arch. int. Pharm., 7: 229.
1901. Stockman and Charteris (Iodid). Brit. Med. J., Nov. 23.
1904. Wiley (Boric Acid). Bur. Chem. Circular No. 13, U. S. Dept. Agr.
1905. Rost (Boric acid, Crit. Bibl.) Arch. int. Pharm., 15: 291.
1901. Vietinghoff-Scheel (Oxalate). Arch. int. Pharm., 8: 225.

1895. Ringer (Calcium, Heart). J. Ph., 18:425.
1901. Sabbatani (Calcium) Arch. it., 36:416.

Acids and Alkalies (Chapter XXVI):
1879. Walter (Acid Poisoning). Schm., 7:148.
1899. Magnus-Levi (Diabetic Coma). Schm., 42:149.
1890. Stadelmann. Ueb. d. Einfl. d. Alkalien auf d. Stoffwechsel. Stuttgart.

Metals (Chapter XXVII):
1874. Boehm and Unterberger (As.). Schm., 2:89.
1898. Stockman and Greig (As. on Bone-marrow). J. Ph., 23:376.
1899. Magnus (As. on Capillaries). Schm., 42:265.
1901. Heffter (Cacodyl). Schm., 46:230.
1902. de Busschler (As. Antidote). Arch. int. Pharm., 10:415.
1894. Macallum (Iron). J. Ph., 16:268.
1896. Hall (Iron). Arch. f. Phys., :49.
1898. v. Bunge (Iron). H.-S., 25:36.
1900. Abderhalden (Iron). Z. B., 39:193.
1903 & 1904. Tartakowski (Iron). Pf., 100:586; 101:423.
1904. Moore (Copper Purif. of Water). Am. J. Phar., 76:553; also critical discussion, Science, 21:603, 1905.
1878. Harnack (Lead). Schm., 9:152.
1886. Jendrássik (Calomel Diuresis). Deut. Arch. Klin. Med., 38:499.
1872. Wegner (P.). Virch., 55:11.
1894. Muenzer (P.). Deut. Arch. Klin. Med., 52:199.
1900. Jacobj (P.). H.-S., 30:174.

Volatile Oils (Chapter XXIX):
1901. Winternitz (Antiseptic). Schm., 45:163.
1903. d'Ormea (Cerebral Circulation). Arch. it., 40:141.
1904. Kionka (Valerian). Arch. int. Pharm., 13:215.

Ivy Poisoning:
1897. Pfaff. J. Exp. Med., 2:181.

Cantharidin:
1885. Mürset. Schm., 19:310.
1900. Ellinger. Schm., 45:89.
1903. v. Fuerth. Vergl. Chem., pp. 352 to 368.

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1904. Sollmann (Critical Bibl.). J. A. M. A., 43:1591.

Stomachics (Chapter XXX):
1890. Penzoldt (Orexin). Ther. Monatsh., :59.
1893. Brandl. Z. B., 29:277.
1904. Borisoff. Schm., 51:362.

Cathartics:
1880. Brandl and Tappeiner. Schm., 26:177.
1903. Magnus. Erg. II J. II:637.

Cholagogues:
1879. Rutherford. Trans. Roy. Soc., Edinb., 29:133.
1897. Pfaff and Balch. J. Exp. Med., 2:49.
1904. Levene, Melvin and Michailkowski. Science, May.

Anthelmintics:
1895 & 1896. Boehm (Aspidium). Schm., 35:1; 38:35.
1904. Jaquet (Aspidium). Ther. Monatsh.
1884. v. Schroeder (Granatum). Schm., 18:381; 19:290.
1885. v. Schroeder (Santonin). Schm., 19:304.
1900. Filehne (Santonin). Pf., 80:96.

Demulcents (Chapter XXXI):
1892. Brandl. Z. B., 29:277.
1902. v. Tappeiner. Arch. int. Pharm., 10:67.

APPENDIX C.

TABLE XVII.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, MOLECULAR WEIGHT AND SOLUBILITY.[1]
(Adapted from U. S. P.)

NAME.	SYMBOL OR FORMULA.	MOLECULAR WEIGHT.[2]	SOLUBILITY[3]: 1 part dissolves in	
			Water.	Alcohol.
Acetanilid	$C_6H_5NH.C_2H_3O$	134.09	179	2.5
Acetic Ether	$C_2H_5.C_2H_3O_2$	87.40	7	a
Acetone	C_3H_6O	57.61	a	a
Acetphenitidin. See Phenacetin.				
Acetophenone (hypnone)	C_8H_8O	....		
Acid, Acetic	$HC_2H_3O_2$	59.58	a	a
" Arsenic	H_3AsO_4	....	2	
" Arsenous	H_3AsO_3	....	80	141
" Benzoic	$HC_7H_5O_2$	121.13	281	1.8
" Boric	H_3BO_3	61.54	18	15.3
" Camphoric	$H_2C_{10}H_{14}O_4$	198.62	125	v. s.
" Carbolic	$C_6H_5.OH$	93.34	19.6	a
" Carbonic	H_2CO_3	61.55	..	..
" Cinnamic	$HC_9H_7O_2$	146.95	..	..
" Citric	$H_3C_6H_5O_7 + H_2O$	208.50	0.54	1.55
" Citric Anhydrous	$H_3C_6H_5O_7$	190.62	s.	s.
" Formic	$HCHO_2$	45.67	s.	s.
" Gallic	$HC_7H_5O_5 + H_2O$	186.65	83.7	4.14
" Gallic Anhydrous	$HC_7H_5O_5$	168.77	s.	s.
" Hydriodic	HI	126.9	a	a
" Hydrobromic	HBr	80.36	a	a
" Hydrochloric	HCl	36.18	a	a
" Hydrocyanic	HCN	26.84	a	a

Acid, Hydrofluoric	HF	19.9	a	a
" Hypophosphorous	HPH_2O_2	65.53	a	a
" Kinic (quinic)	$HC_7H_{11}O_6$	....	..	..
" Lactic	$HC_3H_5O_3$	89.37	a	a
" Meconic	$C_7H_4O_7$	....	sp.	v. s.
" Metaphosphoric	HPO_3	....	..	..
" Molybdic	H_2MoO_4	160.82	..	..
" Nitric	HNO_3	62.57	a	a
" Nitrous	HNO_2	46.69	..	..
" Oleic	$HC_{18}H_{33}O_2$	280.14	ins.	a
" Oxalic	$H_2C_2O_4 + 2H_2O$	125.10	..	..
" Oxalic Anhydrous	$H_2C_2O_4$	89.34	8.17	6.8
" Palmitic	$HC_{16}H_{31}O_2$	....	..	..
" Phosphoric	H_3PO_4	97.29	v. s.	v. s.
" Phosphorous	H_3PHO_3	81.41	..	..
" Picric	$C_6H_2(NO_2)_3OH$	227.41	86	s.
" Pyrophosphoric	$H_4P_2O_7$	....	..	..
" Salicylic	$HC_7H_5O_3$	137.01	.308	2.
" Silicic	H_2SiO_3	....	..	..
" Stearic	$HC_{18}H_{35}O_2$	282.14	ins.	16.6
" Succinic	$H_2C_4H_4O_4$	117.16	19	8
" Sulphanilic	$HC_6H_4(NH_2)SO_3 + 3H_2O$	225.5	..	..
" Sulphanilic Anhydrous		171.86	..	..
" Sulphuric	H_2SO_4	97.35	a	a
" Sulphurous	H_2SO_3	81.47	a	a
" Tannic	$C_{14}H_{10}O_9$	319.66	0.34	0.23
" Tartaric	$H_2C_4H_4O_6$	148.92	0.71	1.67
" Titanic. See Titanic Oxid.		....		
" Trichloracetic	$HC_2Cl_3O_2$	162.12	v. s.	v. s.
" Tungstic. See Tungstic Oxid.		....		

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

[2] Hydrogen (H) = 1.

[3] The solubility of the official chemicals is given for 25°C = 77°F. That of non-official chemicals refers to 15°C = 59°F.

TABLE XVII.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, MOLECULAR WEIGHT AND SOLUBILITY.[1] —*Continued.*

NAME.	SYMBOL OR FORMULA.	MOLECULAR WEIGHT.	SOLUBILITY: 1 part dissolves in	
			Water.	Alcohol.
Acid, Uric	$C_5H_4N_4O_3$	166.91	15000	ins.
" Valerianic	$HC_5H_9O_2$	101.31	30	a
Aconitin	$C_{34}H_{47}NO_{11}$	640.55	3200	22
Agaricin	$C_{16}H_{30}O_5 + H_2O$	317.84	sp.	s.
Alcohol, Amylic	$C_5H_{11}.OH$	87.34	sp.	a
" Ethylic	$C_2H_5.OH$	45.70	a	a
" Methylic	$CH_3.OH$	31.79	a	a
Aldehyd, Acetic	C_2H_4O	43.70	..	s.
" Formic	$CHO.H$	29.79	s.	s.
Allyl Isothiocyanate	$CSNC_3H_5$	98.40		
" Sulphocarbamid. See Thiosinamin.		....		
Alum (Potash-Alum)	$AlK(SO_4)_2 + 12H_2O$	471.02	9	ins.
" (dried)	$AlK(SO_4)_2$	256.46	17	ins.
Aluminium	Al	26.9	ins.	ins.
" and Ammonium Sulphate	$Al_2(SO_4)_3 + (NH_4)_2SO_4 + 24H_2O$	....	s.	..
" Hydrate	$Al_2(OH)_6$	77.54	ins.	ins.
" Oxid	Al_2O_3	101.44	..	..
" Silicate	$H_2Al_2Si_2O_8 + H_2O$	257.12	..	..
" Sulphate	$Al_2(SO_4)_3 + 16H_2O$	625.93	1.	ins.
" Sulphate, Anhydrous	$Al_2(SO_4)_3$	339.85	..	..
Ammonia	NH_3	16.93	a	a.
Ammoniated Mercury. See Mercur-Ammonium chlorid				
Ammonio-Ferric Sulphate (Iron-Alum)	$Fe_2(SO_4)_3 + (NH_4)_2SO_4 + 24H_2O$	....	s.	..
Ammonium Acetate	$NH_4C_2H_3O_2$	76.51	v. s.	..

Ammonium Arsenite (metarsenite)	NH_4AsO_2	124.09	..	..
" Benzoate	$NH_4C_7H_5O_2$	138.06	10.5	25
" Bromid	NH_4Br	97.29	1.2	12.5
" Carbonate (official)	$NH_4HCO_3.NH_4NH_2CO_2$	156.01	4	dec.
" Carbonate (pure)	$(NH_4)_2CO_3$	95.41	..	..
" Chlorid	NH_4Cl	53.11	2	50
" Chloroplatinate	$(NH_4)_2PtCl_6$	440.24	..	..
" Citrate	$(NH_4)_3C_6H_5O_7$	241.41	s.	
" Iodid	NH_4I	143.83	0.6	9
" Lactate	$NH_4C_3H_5O_3$	106.30	s.	
" Molybdate	$(NH_4)_6Mo_7O_{24} + 4H_2O$	1227.32	..	..
" Nitrate	NH_4NO_3	79.50	0.5	20
" Oxalate	$(NH_4)_2C_2O_4 + H_2O$	141.08	3	..
" Oxalate, Anhydrous	$(NH_4)_2C_2O_4$	123.20	..	..
" Persulphate	$(NH_4)_2S_2O_8$	....	s.	..
" Phosphate	$(NH_4)_2HPO_4$	131.15	4	ins.
" Sodium Phosphate	$NH_4.Na.HPO_4 + 4H_2O$	207.62	..	..
" Salicylate	$NH_4C_7H_5O_3$	153.94	0.9	2.3
" Sulphate	$(NH_4)_2SO_4$	131.21	1.3	sp.
" Sulphhydrate	NH_4HS	50.76	s.	..
" Sulphid	$(NH_4)_2S$	67.69	s.	..
" Tartrate	$(NH_4)_2C_4H_4O_6$	182.78	s.	..
" Valerianate	$NH_4C_5H_9O_2$	118.24	v. s.	v. s.
Amyl Acetate	$C_5H_{11}C_2H_3O_2$	....	ins.	a
" Nitrite	$C_5H_{11}NO_2$	116.24	ins.	a
Amylene Hydrate	$C_5H_{12}O$	87.43	..	..
Anethol	$C_{10}H_{12}O$	146.98	..	..
Anilin	$C_6H_5NH_2$	92.39	..	..
Antimonous Chlorid	$SbCl_3$	....	..	..
" Oxid	Sb_2O_3	286.24	n. ins.	ins.
" Sulphid	Sb_2S_3	334.09	ins.	ins.

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XVII.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, MOLECULAR WEIGHT AND SOLUBILITY.[1] —*Continued.*

NAME.	SYMBOL OR FORMULA.	MOLECULAR WEIGHT.	SOLUBILITY: 1 part dissolves in	
			Water.	Alcohol.
Antimony	Sb	119.3	ins.	ins.
" and Potassium Tartrate (dry)	$K(SbO)C_4H_4O_6$	320.96	..	..
" Potassium Tartrate	$2KSbOC_4H_4O_6 + H_2O$	659.80	15.5	ins.
" Pentasulphid	Sb_2S_5	397.75	..	..
Antipyrin. See Phenazone.				
Apomorphin	$C_{17}H_{17}NO_2$	265.16	..	..
" Hydrochlorate	$C_{17}H_{17}NO_2HCl$	301.34	39.5	38.2
Arabin	$2C_6H_{10}O_5 + H_2O$	....	..	..
Argon	Ar	39.6	..	..
Arsenic	As	74.4	ins.	ins.
" Oxid	As_2O_5	....	..	..
" Sulphid	As_2S_5	307.95	..	..
Arsenous Iodid	AsI_3	452.10	12 dec.	28
" Oxid	As_2O_3	196.44	30 to 100	sp.
" Sulphid	As_2S_3	244.29	..	..
Atropin	$C_{17}H_{23}NO_3$	287.04	450	1.46
" Sulphate	$(C_{17}H_{23}NO_3)_2H_2SO_4$	671.43	0.38	3.7
Barium	Ba	136.4	ins.	ins.
" Carbonate	$BaCO_3$	195.95	ins.	n. ins.
" Chlorid	$BaCl_2 + 2H_2O$	242.52	2½	ins.
" Chlorid, Anhydrous	$BaCl_2$	206.76	..	..
" Chromate	$BaCrO_4$	251.62	..	..
" Hydroxid	$Ba(OH)_2 + 8H_2O$	313.20	..	..
" Hydrate, Anhydrous	$Ba(OH)_2$	170.16	n. ins.	..
" Nitrate	$Ba(NO_3)_2$	259.54	12.5	ins.

Barium Peroxid	BaO_2	168.16	..	..
" Sulphate	$BaSO_4$	231.75	ins.	..
" Sulphid	BaS	168.23	..	..
Benzanilid	$C_{13}H_{11}NO$	....	n. ins.	58
Benzene (Benzol)	C_6H_6	77.64	ins.	..
Benzoic Aldehyd	C_7H_6O	105.25	sp. 300	a
Benzosulphinid. See Glycid.				
Benzyl Alcohol	$C_7H_7.OH$	....	..	..
Beryllium. See Glucinum.		....	..	
Betanaphthol. See Naphthol.				
Bismuth	Bi	206.9	ins.	ins.
" Ammon. Citrate				
" Carbonate (basic)	$(BiO)_2CO_3$	505.11	ins.	ins.
" Carbonate (normal)	$Bi_2(CO_3)_3$	....	..	..
" Citrate	$BiC_6H_5O_7$	394.52	ins.	ins.
" Nitrate (normal)	$Bi(NO_3)_3 + 5H_2O$	481.01	..	..
" Oxychlorid	$BiOCl$	....	..	..
" Oxyiodid	$BiOI$	....	ins.	ins.
" Subnitrate	$BiONO_3 + H_2O$	302.22	ins.	ins.
" Subgallate (approximately)	$Bi(OH)_2C_7H_5O_5$	408.43	ins.	ins.
" Subsalicylate (approximately)	$Bi(OH)_2C_7H_5O_3$	376.67	ins.	ins.
" Sulphid	Bi_2S_3	509.29		
" Trioxid	Bi_2O_3	461.44		
Borneol	$C_{10}H_{18}O$	152.98		
Bornyl Acetate	$C_{10}H_{17}C_2H_3O_2$	194.68		
Boron	B	10.9	ins.	ins.
" Trioxid	B_2O_3	69.44	..	..
Bromin	Br	79.36	30	s. (dec.) 28
Bromoform	$CHBr_3$	250.99	sp.	a
Brucin	$C_{23}H_{26}N_2O_4 + 4H_2O$	462.83	750	2
" (dry)	$C_{23}H_{26}N_2O_4$	391.31	..	..

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XVII.— [illegible] TABLE OF CHEMIC DRUGS, THEIR FORMULAS, MOLECULAR WEIGHT AND SOLUBILITY.[1] —*Continued.*

NAME.	SYMBOL OR FORMULA.	MOLECULAR WEIGHT.	SOLUBILITY: 1 part dissolves in	
			Water.	Alcohol.
Cadmium	Cd	119.3	ins.	ins.
" Iodid	CdI_2	320.96	..	..
" Sulphate	$3CdSO_4 + 8H_2O$	659.80	15.5	ins.
" Sulphid	CdS	397.75	..	..
Cæsium	Cs			
Caffein	$C_8H_{10}N_4O_2 + H_2O$	16	..	..
" Anhydrous	$C_8H_{10}N_4O_2$		39.5	38.2
Caffeina Citrata (mixture)			..	..
Calcium	Ca		..	..
" Acetate	$Ca(C_2H_3O_2)_2$			ins.
" Bromid	$CaBr_2$	198.		..
" Carbonate	$CaCO_3$	99.35		..
" Chlorid	$CaCl_2$	110.16		
" Chlorid (crystallized)	$CaCl_2 + 6H_2O$	217.44		
" Fluorid	CaF_2	77.6		
" Hydrate	$Ca(OH)_2$	73.56		
" Hypochlorite	$Ca(OCl)_2$	......		
" Hypophosphite	$CaH_4(PO_2)_2$	168.86	6.5	
" Oxalate	$CaC_2O_4 + H_2O$	145.02	ins.	
" Oxid	CaO	55.68	760	
" Phosphate	$Ca_3(PO_4)_2$	307.98	ins	
" Sulphate	$CaSO_4$	135.15	378	
" Sulphate (crystallized)	$CaSO_4 + 2H_2O$	170.91	..	.
" Sulphid (monosulphid)	CaS	71.63	s.	..
" Tartrate	$CaC_4H_4O_6$	......	..	..

Calomel. See Mercurous Chlorid.				
Camphor	$C_{10}H_{16}O$			
" Monobromated	$C_{10}H_{15}BrO$			
Carbon	C			
" Dioxid	CO_2			
" Disulphid	CS_2			
Carvone	$C_{10}H_{14}O$			
Cerium	Ce			
" Oxalate	$Ce_2(C_2O_4)_3 + 10H_2O$			
" Oxalate (dry)	$Ce_2(C_2O_4)_3$			
Cephælin	$C_{14}H_{19}NO_2$			
Chloral, Anhydrous	C_2HCl_3O			
" Hydrate	$C_2HCl_3O + H_2O$	1		
Chloralformamid	$C_3H_4Cl_3NO_2$	190		
Chlorin	Cl	35.18		
Chloroform	$CHCl_3$	118.45		
Chrome-alum	$Cr_2(SO_4)_3 + K_2SO_4 + 24H_2O$	......		
Chromium	Cr	51.7		
" Sesquioxid	Cr_2O_3	151.04		
" Trioxid	CrO_3	99.34	v.	
Chrysarobin	$C_{30}H_{26}O_7$	494.47	481	
Cinchonidin	$C_{19}H_{22}N_2O$	292.03	2500	
" Salicylate	$C_{19}H_{22}N_2O.C_7H_6O_3$	429.04	..	
" Sulphate	$(C_{19}H_{22}N_2O)_2H_2SO_4 + 3H_2O$	735.05	63	2
" Sulphate (dry)	$(C_{19}H_{22}N_2O)_2H_2SO_4$	681.41	s.	s.
Cinchonin	$C_{19}H_{22}N_2O$	292.03	3760	116
" Sulphate	$(C_{19}H_{22}N_2O)_2H_2SO_4 + 2H_2O$	717.17	58	10
" Sulphate (dry)	$(C_{19}H_{22}N_2O)_2H_2SO_4$	681.41	s.	s.
Cineol. See Eucalyptol.				
Cinnamic Aldehyd	C_9H_8O	131.07	sp.	a
Citral	$C_{10}H_{16}O$	150.98	..	..

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XVII.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, MOLECULAR WEIGHT AND SOLUBILITY.[1]
—*Continued.*

NAME.	SYMBOL OR FORMULA.	MOLECULAR WEIGHT.	SOLUBILITY: 1 part dissolves in	
			Water.	Alcohol.
Cadmium	Cd	111.6	..	..
" Iodid	CdI_2	....	2	sol.
" Sulphate	$3CdSO_4 + 8H_2O$	763.89	v. s.	v. s.
" Sulphid	CdS	143.43	..	..
Cæsium	Cs	131.9	..	..
Caffein	$C_8H_{10}N_4O_2 + H_2O$	210.64	45.6	53.2
" Anhydrous	$C_8H_{10}N_4O_2$	192.76	..	..
Caffeina Citrata (mixture)		....	25	..
Calcium	Ca	39.8	ins.	ins.
" Acetate	$Ca(C_2H_3O_2)_2$	....	s.	s.
" Bromid	$CaBr_2$	198.52	0.5	1
" Carbonate	$CaCO_3$	99.35	ins.	ins.
" Chlorid	$CaCl_2$	110.16	1.3	8
" Chlorid (crystallized)	$CaCl_2 + 6H_2O$	217.44	..	..
" Fluorid	CaF_2	77.6	..	..
" Hydrate	$Ca(OH)_2$	73.56	sp.	..
" Hypochlorite	$Ca(OCl)_2$	......	..	..
" Hypophosphite	$CaH_4(PO_2)_2$	168.86	6.5	ins.
" Oxalate	$CaC_2O_4 + H_2O$	145.02	ins.	ins.
" Oxid	CaO	55.68	760	ins.
" Phosphate	$Ca_3(PO_4)_2$	307.98	ins	ins.
" Sulphate	$CaSO_4$	135.15	378	ins.
" Sulphate (crystallized)	$CaSO_4 + 2H_2O$	170.91	..	..
" Sulphid (monosulphid)	CaS	71.63	s.	..
" Tartrate	$CaC_4H_4O_6$	......	..	..

Calomel. See Mercurous Chlorid.				
Camphor	$C_{10}H_{16}O$	150.98	sp.	v. s.
" Monobromated	$C_{10}H_{15}BrO$	229.34	n. ins.	v. s.
Carbon	C	11.91	ins.	ins.
" Dioxid	CO_2	43.67	s.	s.
" Disulphid	CS_2	75.57	526	v. s.
Carvone	$C_{10}H_{14}O$	148.98	..	..
Cerium	Ce	139.2	ins.	ins.
" Oxalate	$Ce_2(C_2O_4)_3 + 10H_2O$	719.22	ins.	ins.
" Oxalate (dry)	$Ce_2(C_2O_4)_3$	540.42	ins.	ins.
Cephælin	$C_{14}H_{19}NO_2$	231.43	..	..
Chloral, Anhydrous	C_2HCl_3O	146.24	v. s.	v. s.
" Hydrate	$C_2HCl_3O + H_2O$	164.12	v. s.	v. s.
Chloralformamid	$C_3H_4Cl_3NO_2$	190.96	18.7	1.3
Chlorin	Cl	35.18	v. s.	..
Chloroform	$CHCl_3$	118.45	200	a
Chrome-alum	$Cr_2(SO_4)_3 + K_2SO_4 + 24H_2O$	......	s.	..
Chromium	Cr	51.7	ins.	ins.
" Sesquioxid	Cr_2O_3	151.04	s.	..
" Trioxid	CrO_3	99.34	v. s.	dec.
Chrysarobin	$C_{30}H_{26}O_7$	494.47	4812	308
Cinchonidin	$C_{19}H_{22}N_2O$	292.03	2500	20
" Salicylate	$C_{19}H_{22}N_2O.C_7H_6O_3$	429.04	..	..
" Sulphate	$(C_{19}H_{22}N_2O)_2H_2SO_4 + 3H_2O$	735.05	63	72
" Sulphate (dry)	$(C_{19}H_{22}N_2O)_2H_2SO_4$	681.41	s.	s.
Cinchonin	$C_{19}H_{22}N_2O$	292.03	3760	116
" Sulphate	$(C_{19}H_{22}N_2O)_2H_2SO_4 + 2H_2O$	717.17	58	10
" Sulphate (dry)	$(C_{19}H_{22}N_2O)_2H_2SO_4$	681.41	s.	s.
Cineol. See Eucalyptol.				
Cinnamic Aldehyd	C_9H_8O	131.07	sp.	a
Citral	$C_{10}H_{16}O$	150.98	..	..

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XVII.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, MOLECULAR WEIGHT AND SOLUBILITY.[1]—*Continued.*

NAME.	SYMBOL OR FORMULA.	MOLECULAR WEIGHT.	SOLUBILITY: 1 part dissolves in	
			Water.	Alcohol.
Cinnabar. See Mercuric Sulphid.				
Cobalt	Co	58.56	ins.	ins.
Cobaltous Nitrate	$Co(NO_3)_2 + 6H_2O$	288.98	s.	..
" Sulphate	$CoSO_4 + 7H_2O$	279.07	..	..
Cocain	$C_{17}H_{21}NO_4$	300.92	600	5
" Hydrochlorate	$C_{17}H_{21}NO_4HCl$	337.10	0.4	2.6
Codein	$C_{18}H_{21}NO_3 + H_2O$	314.83	88	1.6
" Anhydrous	$C_{18}H_{21}NO_3$	296.95	..	..
" Phosphate	$C_{18}H_{21}NO_3.H_3PO_4 + 2H_2O$	430.0	2.25	261
" Phosphate, Anhydrous	$C_{18}H_{21}NO_3.H_3PO_4$	394.24	..	..
" Sulphate	$(C_{18}H_{21}NO_3)_2H_2SO_4 + 5H_2O$	780.65	30	1035
" Sulphate, Anhydrous	$(C_{18}N_{21}NO_3)_2H_2SO_4$	691.25	..	..
Colchicin	$C_{22}H_{25}NO_6$	396.23	22	v. s.
Columbium	Cb	93.3	..	..
Coniin	$C_8H_{17}N$	126.21	100	v. s.
Copper	Cu	63.1	ins.	ins.
" Acetate	$Cu(C_2H_3O_2)_2 + H_2O$	......	15	16
" Acetate (basic)	$Cu(C_2H_3O_2)_2 + CuO + 6H_2O$	......	..	..
" Carbonate (basic)	$CuCO_3 + Cu(OH)_2$	......	n. ins	..
" Sulphate	$CuSO_4 + 5H_2O$	247.85	2.2	400
" Sulphate (ammoniacal)	$CuSO_4 + 4NH_3 + H_2O$	244.05	s.	s.
Corrosive Sublimate. See Mercuric Chlorid.				
Creosote		......	140	a
Cresol (cresylic acid)	C_7H_8O	107.25	60	a
Cupric Oxid	CuO	......	ins.	ins.

Cupric Sulphate. See Copper sulphate.				
" Sulphate (dry)	$CuSO_4$	158.45	s.	s.
" Sulphid	CuS	94.93	..	..
" Tartrate	$CuC_4H_4O_6 + 3H_2O$	263.66	s.	s.
Cuprous Oxid	Cu_2O	142.08	ins.	ins.
Cyanogen	$(CN)_2$	51.68	dec.	..
Didymium	Di	......	..	..
Diethylsulphon-Dimethylmethane (sulphonal)	$C_7H_{16}S_2O_4$	......	..	..
Diiodparaphenol Sulphonic Acid (soziodol)	$C_6H_4I_2SO_4$	......	..	..
Dimethyl Phenyl-Pyrazolon (antipyrin)	$C_{11}H_{12}N_2O$	......	1	1
Diphenylamin	$(C_6H_5)_2NH$	167.85	..	..
Dithymol Diiodid (aristol)	$C_{20}H_{24}O_2I_2$	545.76	ins.	sp.
Elaterin	$C_{20}H_{28}O_5$	345.60	ins.	262
Emetin	$C_{15}H_{21}NO_2$	245.34	..	..
Erbium	E	164.8	..	..
Ether, Ethylic (common sulphuric)	$(C_2H_5)_2O$	73.52	10	a
Ethyl Acetate. See Acetic Ether.			8	a
" Bromid	C_2H_5Br	......	sp.	a
" Carbamate (urethane)	$C_3H_7NO_2$	88.42	< 1	0.6
" Chlorid	C_2H_5Cl	64.00	sp.	a
" Nitrite	$C_2H_5NO_2$	74.51	sp. s.	a
Ethylene	C_2H_4	......	..	..
Eucain Beta Hydrochlorid	$C_{19}H_{27}NO_4.HCl + H_2O$	......	35	..
" " Lactate		......	4	..
Eucalyptol	$C_{10}H_{18}O$	152.98	n. ins.	a
Eugenol	$C_{10}H_{12}O_2$	162.86	sp.	v. s.
Exalgin (methyl acetanilid)	$C_9H_{11}NO$	148.00	..	..
Ferric Acetate	$Fe(C_2H_3O_2)_3$	231.24	4	s.
" Ammonium Sulphate	$Fe(NH_4)(SO_4)_2 + 12H_2O$	478.69	2.7	ins.
" Ammonium Sulphate (dry)	$Fe(NH_4)(SO_4)_2$	264.13	s.	ins.
" Chlorid	$FeCl_3 + 6H_2O$	268.32	v. s.	v. s.

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XVII.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, MOLECULAR WEIGHT AND SOLUBILITY.[1]
—*Continued.*

NAME.	SYMBOL OR FORMULA.	MOLECULAR WEIGHT.	SOLUBILITY: 1 part dissolves in	
			Water.	Alcohol.
Ferric Chlorid (dry)	$FeCl_3$	161.04	v. s.	v. s.
" Citrate	$Fe_2(C_6H_5O_7)_2 + 6H_2O$	......	s.	ins.
" Hydrate	$Fe(OH)_3$	106.14	ins.	ins.
" Hypophosphite	$Fe(H_2PO_2)_3$	249.09	2300	ins.
" Nitrate	$Fe(NO_3)_3$	240.21	s.	s.
" Oxid (sesquioxid)	Fe_2O_3	158.64	ins.	ins.
" Phosphate	$Fe(PO_4)$	149.79	v. s.	ins.
" Pyrophosphate	$(Fe_2)_2(P_2O_7)_3$	740.10	v. s.	ins.
" Sulphate (basic)	$Fe_4O(SO_4)_5$	......	s.	ins.
" Sulphate (normal)	$Fe_2(SO_4)_3$	397.05	s.	ins.
Ferricyanic Acid	$H_6Fe_2(CN)_{12}$	......	..	..
Ferrocyanic Acid	$H_4Fe(CN)_6$	......	..	..
Ferrous Bromid	$FeBr_2 + 6H_2O$	321.50	..	..
" Bromid (anhydrous)	$FeBr_2$	214.22	s.	s.
" Carbonate	$FeCO_3$	115.05	sp.	ins.
" Hydrate	$Fe(OH)_2$	89.26	ins.	ins.
" Iodid	FeI_2	307.30	s.	s.
" Lactate	$Fe(C_3H_5O_3)_2 + 3H_2O$	285.88	40	ins.
" Oxalate	$FeC_2O_4 + H_2O$	......	n. ins.	ins.
" Oxid	FeO	71.38	ins.	ins.
" Sulphate	$FeSO_4 + 7H_2O$	276.01	0.9	ins.
" Sulphate (anhydrous)	$FeSO_4$	150.85	s.	ins.
" Sulphate (dried)	$FeSO_4 + H_2O$	......	1.8	ins.
" Sulphid	FeS	87.33	ins.	ins.

Fluorin	F	18.9	..	..
Gadolinium	Gd	155.0	..	..
Gallium	Ga	69.5	..	..
Germanium	Ge	71.9	..	..
Glucid (saccharin) (benzosulphinid)	$C_7H_5SO_3N$	181.77	250	25
Glucinum	Gl	9.03	..	..
Glucose	$C_6H_{12}O_6$	178.74	s.	sp.
Glycerin	$C_3H_5(OH)_3$	91.37	a.	a
Glyceryl Trinitrate (nitroglycerin)	$C_3H_5(NO_3)_3$	225.44	sp.	s.
Glycol	$C_2H_4(OH)_2$	......	..	..
Gold	Au	195.7	ins.	ins.
" and Sodium Chlorid	$AuCl_3 + NaCl$	......	v. s.	dec.
" Chlorid	$AuCl_3$	301.24	s.	s.
Grape-sugar. See Glucose.				
Guaiacol	$C_7H_8O_2$	123.13	53	a
" Carbonate	$(C_7H_7O)_2\ CO_3$	272.05	ins.	48
Helium	He	4.0	..	..
Heroin Hydrochlorid	$C_{17}H_{17}(C_2H_3O_2)_2NO.HCl$	402.62	s.	s.
Hexamethylenamin	$C_6H_{12}N_4$	139.18	1.5	10
Homatropin Hydrobromid	$C_{16}H_{21}NO_3HBr$	353.49	5.7	32.5
Hydrastin	$C_{21}H_{21}NO_6$	380.32	n. ins.	135
" Hydrochlorid	$C_{21}H_{21}NO_6HCl$	416.50	..	..
Hydrastinin Hydrochlorid	$C_{11}H_{11}NO_2HCl$	223.88	v. s.	v. s.
Hydrogen	H	1.00	..	..
" Dioxid	H_2O_2	33.76	a	a
" Oxid (water)	H_2O	......	..	..
" Sulphid	H_2S	33.83	s.	s.
Hydroquinone	$C_6H_6O_2$	......	20	v. s.
Hyoscin Hydrobromid	$C_{17}H_{21}NO_4HBr + 3H_2O$	434.92	1.5	16
" Hydrobromid (dry)	$C_{17}H_{21}NO_4HBr$	381.28	s.	s.
Hyoscyamin	$C_{17}H_{23}NO_3$	287.04	500	v. s.

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XVII.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, MOLECULAR WEIGHT AND SOLUBILITY.[1] —*Continued.*

NAME.	SYMBOL OR FORMULA.	MOLECULAR WEIGHT.	SOLUBILITY: 1 part dissolves in	
			Water.	Alcohol.
Hyoscyamin Hydrobromid	$C_{17}H_{23}NO_3HBr$	367.40	v. s.	2
" Sulphate	$(C_{17}H_{23}NO_3)_2H_2SO_4$	671.43	v. s.	6.4
Indigo-blue	C_8H_5NO	......	. .	. .
Indium	In	113.1	. .	. .
Iodrosin	$C_{20}H_8I_4O_5$	829.20	. .	. .
Iodin	I	125.90	5000	10
Iodoform	CHI_3	390.61	9391	46.7
Iodol (tetraiodopyrrol)	C_4HI_4N	566.17	4900	9
Iridium	Ir	191.5	. .	. .
Iron	Fe	55.5	ins.	ins.
" Compounds. See Ferrous and Ferric.				
Lactose. See Sugar of Milk.				
Krypton	Kr	81.2	. .	. .
Lanthanum	La	137.9	. .	. .
Lead	Pb	205.35	ins.	ins.
" Acetate	$Pb(C_2H_3O_2)_2 + 3H_2O$	376.15	2.	30
" Acetate (basic)	$Pb_2O(C_2H_3O_2)_2$	543.74	s.	s.
" Acetate (dry)	$Pb(C_2H_3O_2)_2$	322.51	s.	s.
" Carbonate (official)	$2(PbCO_3) + Pb(OH)_2$	768.91	ins.	ins.
" Carbonate (pure)	$PbCO_3$	264.90	ins.	ins.
" Chlorid	$PbCl_2$	275.71	ins.	ins.
" Chromate	$PbCrO_4$	320.57	ins.	ins.
" Dioxid	PbO_2	......	n. ins.	n. ins.
" Iodid	PbI_2	457.15	1,300	sp.
" Nitrate	$Pb(NO_3)_2$	328.40	1.85	n. ins.

Lead Oxid	PbO	221.23	n. ins.	ins.
" Red Oxid	Pb_3O_4	......	ins.	ins.
" Sulphate	$PbSO_4$	300.70	ins.	ins.
" Sulphid	PbS	237.18	ins.	ins.
Lime. See Calcium Oxid.				
Limonene	$C_{10}H_{16}$	135.10	..	..
Linalyl Acetate	$C_{10}H_{17}C_2H_3O_2$	194.68	..	..
Lithium	Li	6.98	dec.	dec.
" Benzoate	$LiC_7H_5O_2$	127.11	3	13
" Bromid	$LiBr$	86.34	0.6	v. s.
" Carbonate	Li_2CO_3	73.51	75	ins.
" Citrate	$Li_3C_6H_5O_7 + 4H_2O$	280.08	2	n. ins.
" Phosphate	Li_3PO_4	115.23	..	..
" Salicylate	$LiC_7H_5O_3$	142.99	v. s.	v. s.
Magnesium	Mg	24.18	ins.	ins.
" Carbonate (official)	$(MgCO_3)_4.Mg(OH)_2 + 5H_2O$	482.26	n. ins.	ins.
" Carbonate (pure)	$MgCO_3$	83.73	n. ins.	ins.
" Oxid (magnesia)	MgO	40.06	n. ins.	ins.
" Pyroarsenate	$Mg_2As_2O_7$	308.32	..	..
" Pyrophosphate	$Mg_2P_2O_7$	221.06	..	..
" Sulphate	$MgSO_4 + 7H_2O$	244.69	0.85	ins.
" Sulphate (dry)	$MgSO_4$	119.53	s.	ins.
" Sulphite	$MgSO_3 + 6H_2O$	.. .	40	ins.
Manganese	Mn	54.6	ins.	ins.
" Dioxid	MnO_2	86.36	ins.	ins.
" Hypophosphite	$Mn(PH_2O_2)_2 + H_2O$	201.54	6.6	n. ins.
Manganous Oxid	MnO	70.48	..	..
" Sulphate, anhydrous	$MnSO_4$	149.95	..	..
" Sulphate	$MnSO_4 + 4H_2O$	221.47	0.7	ins.
Menthol	$C_{10}H_{19}OH$	154.98	sl.	v. s.

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XVII.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, MOLECULAR WEIGHT AND SOLUBILITY.[1] —*Continued.*

NAME.	SYMBOL OR FORMULA.	MOLECULAR WEIGHT.	SOLUBILITY: 1 part dissolves in	
			Water.	Alcohol.
Menthyl Acetate	$C_{10}H_{19}C_2H_3O_2$	196.68	..	..
Mercur-Ammonium Chlorid	NH_2HgCl	249.61	ins.	ins.
Mercuric Chlorid	$HgCl_2$	268.86	13	3
" Cyanid	$Hg(CN)_2$	250.18	12.8	15
" Iodid	HgI_2	450.30	n. ins.	116
" Nitrate	$Hg(NO_3)_2 + 4H_2O$	393.16	s.	..
" Nitrate, Anhydrous	$Hg(NO_3)_2$	321.64	..	..
" Oxid	HgO	214.38	ins.	ins.
" Potassium Iodid	$HgI_2 + 2KI$	779.82	s.	..
" Sulphate (normal)	$HgSO_4$	293.85	..	..
" Sulphate (yellow or basic)	$Hg(HgO)_2SO_4$	722.61	2000	ins.
" Sulphid	HgS	230.33	ins.	ins.
Mercurous Chlorid	$HgCl$	233.68	ins.	ins.
" Iodid	HgI	324.40	ins.	ins.
" Nitrate	$Hg(NO_3) + H_2O$	277.95	..	..
" Sulphate	Hg_2SO_4	492.35	..	..
Mercury	Hg	198.5	ins.	ins.
Methylacetanilid	$C_6H_5N(CH_3)C_2H_3O$	148.00	..	
Methyl Alcohol. See Alcohol, Methylic.				
" Iodid	CH_3I	140.81	..	..
" Salicylate	$CH_3C_7H_5O_3$	150.92	sp.	a
Methylen Blue. See Methylthionin Hydrochlorid.				
Methylthionin Hydrochlorid	$C_{16}H_{18}N_3SCl$	317.36	v. s.	v. s.
Methyl Orange	$NaC_{14}H_{14}N_3SO_3$	324.88	..	..

Methylene Chlorid	CH_2Cl_2	......	..	..
Molybdenum	Mo	95.3	ins.	ins.
Molybdic Oxid	MoO_3	......	..	
Morphin	$C_{17}H_{19}NO_3 + H_2O$	300.92	3330	168
" (dry)	$C_{17}H_{19}NO_3$	283.04	..	
" Acetate	$C_{17}H_{19}NO_3.HC_2H_3O_2 + 3H_2O$	396.26	2.25	21.6
" Hydrochlorate	$C_{17}H_{19}NO_3HCl + 3H_2O$	372.86	17.2	42.
" Hydrochlorate (dry)	$C_{17}H_{19}NO_3HCl$	319.22	..	..
" Sulphate	$(C_{17}H_{19}NO_3)_2H_2SO_4 + 5H_2O$	752.83	15.3	465
" Sulphate (dry)	$(C_{17}H_{19}NO_3)_2H_2SO_4$	663.43	..	..
Naphtalin	$C_{10}H_8$	127.10	ins.	13
Naphtol Beta	$C_{10}H_7(OH)$	142.98	950	0.61
Naphthylamin Acetate	$C_{10}H_7NH_2HC_2H_3O_2$	201.61	..	..
Narcein	$C_{23}H_{29}NO_9$	......	1200	800
Narcotin	$C_{22}H_{23}NO_7$	......	n. ins.	80
Neodymium	Nd	142.5	..	..
Neon	Ne	19.9	..	..
Nickel	Ni	58.3	ins.	ins.
Nickelous Oxid	NiO	74.18	..	..
" Sulphate	$NiSO_4 + 7H_2O$	278.81	..	..
Nicotin	$C_{10}H_{14}N_2$		s.	v. s.
Niobium. See Columbium.				
Nitrogen	N	13.93	..	..
" Dioxid	NO	29.81	..	..
Nitroglycerin. See Glyceryl Trinitrate.				
Orthoform	$C_8H_9NO_3$	165.85	..	..
Osmium	Os	189.6	ins.	ins.
Oxygen	O	15.88	..	..
Palladium	Pd	105.7	ins.	ins.
Palladous Chlorid	$PdCl_2$	176.06	..	..
Paraldehyd	$C_6H_{12}O_3$	131.10	8	a

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XVII.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, MOLECULAR WEIGHT AND SOLUBILITY.[1] —*Continued.*

NAME.	SYMBOL OR FORMULA.	MOLECULAR WEIGHT.	SOLUBILITY: I part dissolves in	
			Water.	Alcohol.
Paramorphin. See Thebain.				
Phenacetin	$C_{10}H_{13}NO_2$	117.79	925	12
Phenazone (antipyrin)	$C_{11}H_{12}N_2O$	186.75	<1	1
Phenol. See Carbolic Acid.				
Phenolphthalein	$C_{20}H_{14}O_4$	315.72	..	..
Phenyl Salicylate. See Salol.				
Phosphorus	P	30.77	ins.	350
" Oxychlorid	$POCl_3$	......	..	..
" Pentachlorid	PCl_5	......	..	..
" Trichlorid	PCl_3	......	..	..
Physostigmin	$C_{15}H_{21}N_3O_2$	273.20	..	..
" Sulphate	$(C_{15}H_{21}N_3O_2)_2H_2SO_4$	643.75	v. s.	v. s.
" Salicylate	$C_{15}H_{21}N_3O_2C_7H_6O_3$	410.21	72.5	12.7
Picrotoxin	$C_{30}H_{34}O_{13}$	597.74	240	9
Pilocarpin	$C_{11}H_{16}N_2O_2$	206.63	..	..
" Nitrate	$C_{11}H_{16}N_2O_2.HNO_3$	269.20	4	60
" Hydrochlorate	$C_{11}H_{16}N_2O_2HCl$	242.81	0.3	2.3
Piperazin	$C_4H_{10}N_2$	......	v. s.	..
Piperin	$C_{17}H_{19}NO_3$	283.04	ins.	15
Platinic Chlorid	$PtCl_4$	334.02	s.	..
Platinum	Pt	193.3	ins.	ins.
Potassium	K	38.86	dec.	..
" Acetate	$KC_2H_3O_2$	97.44	0.4	2
" Acid Carbonate	$KHCO_3$	99.41	3	n. ins.
" Acid Oxalate (salt of sorrel)	KHC_2O_4	......	s.	ins.

Potassium and Sodium Tartrate	$KNaC_4H_4O_6 + 4H_2O$	280.18	1.2	n. ins.
" Sodium Tartrate, Anhydrous	$KNaC_4H_4O_6$	208.66	..	..
" Arsenite (metarsenite)	$KAsO_2$	145.02	v. s.	sp.
" Benzoate	$KC_7H_5O_2 + 3H_2O$	212.63	..	..
" Benzoate, Anhydrous	$KC_7H_5O_2$	158.99	..	..
" Bichromate	$K_2Cr_2O_7$	292.28	9	ins.
" Bisulphate	$KHSO_4$	135.21	..	..
" Bitartrate	$KHC_4H_4O_6$	186.78	200	sp.
" Bromate	$KBrO_3$	165.86	..	..
" Bromid	KBr	118.22	1.5	180
" Carbonate	K_2CO_3	137.27	0.91	ins.
" Chlorate	$KClO_3$	121.68	16	sp.
" Chlorid	KCl	74.04	3	s.
" Chloroplatinate	K_2PtCl_6	482.10	..	..
" Chromate	K_2CrO_4	192.94	s.	..
" Citrate	$K_3C_6H_5O_7 + H_2O$	322.08	0.5	sp.
" Citrate, Anhydrous	$K_3C_6H_5O_7$	304.20	..	..
" Cyanid	KCN	64.70	2	sp.
" Ferricyanid	$K_3Fe(CN)_6$	327.12	4	sp.
" Ferrocyanid	$K_4Fe(CN)_6 + 3H_2O$	419.62	4	ins.
" Ferrocyanid, Anhydrous	$K_4Fe(CN)_6$	365.98	..	..
" Hydrate	KOH	55.74	0.4	2
" Hypophosphite	KH_2PO_2	103.39	0.5	7
" Iodid	KI	164.76	0.7	12
" Lactate	$KC_3H_5O_3$	127.23	..	..
" Nitrate	KNO_3	100.43	3.6	sp.
" Permanganate	$KMnO_4$	156.98	15	dec.
" Phosphate	K_2HPO_4	173.01	..	..
" Salicylate	$KC_7H_5O_3$	174.87	..	..
" Sodium Tartrate, anhydrous	$KNaC_4H_4O_6$	208.66	..	..
" Sulphate	K_2SO_4	173.07	9	ins.

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XVII.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, MOLECULAR WEIGHT AND SOLUBILITY.[1] —*Continued.*

NAME.	SYMBOL OR FORMULA.	MOLECULAR WEIGHT.	SOLUBILITY: 1 part dissolves in	
			Water.	Alcohol.
Potassium Sulphite	$K_2SO_3 + 2H_2O$	192.95	s.	..
" Sulphite, Anhydrous	K_2SO_3	157.19	..	..
" Sulphocyanate	KSCN	96.53	s.	..
" Tartrate	$(K_2C_4H_4O_6)_2 + H_2O$	467.16	1	ins.
" Tartrate, Anhydrous	$K_2C_4H_4O_6$	224.64	..	..
Praseodymium	Pr	139.4	..	..
Prussian Blue (ferric ferrocyanid)	$Fe_4(Fe(CN)_6)_3$	......	n. ins.	ins.
Prussic Acid. See Acid, Hydrocyanic.				
Pyridin	C_5H_5N	......	s.	v. s.
Pyrogallol (pyrogallic acid)	$C_6H_3(OH)_3$	125.10	1.6	1
Pyrrol	C_4H_5N	......	..	..
Quinidin	$C_{20}H_{24}N_2O_2$	......	2000	20
" Sulphate	$(C_{20}H_{24}N_2O_2)_2H_2SO_4 + 2H_2O$	776.75	100	8
" Sulphate (dry)	$(C_{20}H_{24}N_2O_2)_2H_2SO_4$	740.99	s.	s.
Quinin	$C_{20}H_{24}N_2O_2 + 3H_2O$	375.46	1550	0.6
" (dry)	$C_{20}H_{24}N_2O_2$	321.82	1750	0.6
" Bisulphate	$(C_{20}H_{24}N_2O_2)H_2SO_4 + 7H_2O$	544.33	8.5	18
" Bisulphate (dry)	$C_{20}H_{24}N_2O_2H_2SO_4$	419.17	s.	s.
" Hydrobromid	$C_{20}H_{24}N_2O_2HBr + H_2O$	420.06	40	0.67
" Hydrobromid (dry)	$C_{20}H_{24}N_2O_2HBr$	402.18	s.	s.
" Hydrochlorid	$C_{20}H_{24}N_2O_2HCl + 2H_2O$	393.76	18	0.6
" Hydrochlorid (dry)	$C_{20}H_{24}N_2O_2HCl$	358.00	s.	s.
" Salicylate	$2C_{20}H_{24}N_2O_2.C_7H_6O_3 + H_2O$	935.54	77	11
" Sulphate	$(C_{20}H_{24}N_2O_2)_2H_2SO_4 + 7H_2O$	866.15	720	86
" Sulphate (dry)	$(C_{20}H_{24}N_2O_2)_2H_2SO_4$	740.99	s.	s.

Quinin Valerianate	$C_{20}H_{24}N_2O_2C_5H_{10}O_2 + H_2O$	441.01	100	5
Quinolin	C_9H_7N	......	s.	v. s.
Radium	Ra	223.0	..	..
Resorcin	$C_6H_6O_2$	109.22	0.5	0.5
Rhodium	Rh	102.2	..	..
Rubidium	Rb	84.8	..	..
Ruthenium	Ru	100.9	..	..
Saccharin. See Benzosulphinidum.				
Safrol	$C_{10}H_{10}O_2$	160.86	..	..
Salicin	$C_{13}H_{18}O_7$	283.99	21	71
Salol (phenyl salicylate)	$C_6H_5C_7H_5O_3$	212.47	2333	5
Samarium	Sm	148.9	..	..
Santalol	$C_{15}H_{26}O$	220.53	..	..
Santonin	$C_{15}H_{18}O_3$	244.29	5300	34
Scandium	Sc	43.8	..	..
Scopolamin. See Hyoscin.				
Selenium	Se	78.6	..	..
Silica. See Silicic Oxid.				
Silicic Oxid	SiO_2	59.96	..	..
Silicon	Si	28.2	..	..
Silver	Ag	107.12	ins.	ins.
" Bromid	AgBr	186.48	ins.	ins.
" Chlorid	AgCl	142.30	ins.	ins.
" Cyanid	AgCN	132.96	ins.	ins.
" Iodid	AgI	233.02	ins.	ins.
" Nitrate	$AgNO_3$	168.69	0.54	24
" Nitrate (ammoniacal)	$AgNO_3 + 2NH_3$	......	..	..
" Oxid	Ag_2O	230.12	n. ins.	ins.
" Sulphate	Ag_2SO_4	309.59	200	..
" Sulphid	Ag_2S	246.07	..	..
Sodium	Na	22.88	dec.	..

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XVII.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, MOLECULAR WEIGHT AND SOLUBILITY.[1] —*Continued.*

NAME.	SYMBOL OR FORMULA.	MOLECULAR WEIGHT.	SOLUBILITY: 1 part dissolves in	
			Water.	Alcohol.
Sodium Acetate	$NaC_2H_3O_2 + 3H_2O$	135.10	1.	23
" Acetate (dry)	$NaC_2H_3O_2$	81.46	v. s.	s.
" Arsenate	$Na_2HAsO_4 + 7H_2O$	309.84	1.2	sp.
" Arsenate (dry)	Na_2HAsO_4	184.68	3	sp.
" Arsenite (metarsenite)	$NaAsO_2$	129.04	s.	sp.
" Benzoate	$NaC_7H_5O_2$	143.01	1.6	43
" Bicarbonate	$NaHCO_3$	83.43	12(15°C)	ins.
" Bisulphite	$NaHSO_3$	103.35	20.4	70
" Bitartrate	$NaHC_4H_4O_6 + H_2O$	188.68	3.5	ins.
" Borate	$Na_2B_4O_7 + 10H_2O$	379.32	s.	ins.
" Borate (dry)	$Na_2B_4O_7$	200.52	s.	ins.
" Bromate	$NaBrO_3$	149.88	s.	sp.
" Bromid	$NaBr$	102.24	1.7	12.5
" Carbonate	$Na_2CO_3 + 10H_2O$	284.11	1.6	ins.
" Carbonate (dry)	Na_2CO_3	105.31	v. s.	ins.
" Carbonate, Monohydrated	$Na_2CO_3 + H_2O$	123.19	2.9	ins.
" Chlorate	$NaClO_3$	105.70	1.	100
" Chlorid	$NaCl$	58.06	2.8	n. ins.
" Citrate	$2Na_3C_6H_5O_7 + 11H_2O$	709.20	1.1	sp. s.
" Citrate (dry)	$Na_3C_6H_5O_7$	256.26	v. s.	sp. s.
" Cobaltic Nitrite	$Co_2(NO_2)_6 6NaNO_2 + H_2O$	820.56	s.	. .
" Hydrate	$NaOH$	39.76	1	v. s.
" Hypophosphite	$NaH_2PO_2 + H_2O$	105.29	1	25
" Hyposulphite (dry)	$Na_2S_2O_3$	157.06	s.	s.
" Hyposulphite (thiosulphate)	$Na_2S_2O_3 + 5H_2O$	240.46	0.35	ins.

Sodium Iodid	NaI	148.78	0.5	3
" Lactate	$NaC_3H_5O_3$	111.25	v. s.	v. s.
" Molybdate	$Na_2MoO_4 + H_2O$	......	..	..
" Nitrate	$NaNO_3$	84.45	1.1	100
" Nitrite	$NaNO_2$	68.57	1.4	sl.
" Nitroprussid	$Na_2Fe(NO)(CN)_5 + 2H_2O$	296.03	s.	..
" Phosphate	$Na_2HPO_4 + 12H_2O$	355.61	5.5	ins.
" Phosphate (dry)	Na_2HPO_4	141.05	s.	ins.
" Pyrophosphate	$Na_4P_2O_7 + 10H_2O$	443.02	11.5	ins.
" Pyrophosphate (dry)	$Na_4P_2O_7$	264.22	..	..
" Salicylate	$NaC_7H_5O_3$	158.89	0.8	5.5
" Santoninate	$2NaC_{15}H_{19}O_4 + 7H_2O$	......	3	12
" Sulphate	$Na_2SO_4 + 10H_2O$	319.91	2.8(15°C)	ins.
" Sulphate (dry)	Na_2SO_4	141.11	s.	ins.
" Sulphite	$Na_2SO_3 + 7H_2O$	250.39	2	sp.
" Sulphite (dry)	Na_2SO_3	125.23	s.	sp.
" Sulphocarbolate	$NaC_6H_5SO_4 + 2H_2O$	230.45	4.8	130
" Tartrate	$Na_2C_4H_4O_6 + 2H_2O$	228.44	5	ins.
" Thiosulphate. See Hyposulphite.				
Soziodol (soziodolic acid)	$C_6H_2I_2(OH)SO_3H$	......	..	..
Spartein Sulphate	$C_{15}H_{26}N_2H_2SO_4 + 5H_2O$	419.26	1.1	2.4
" Sulphate (dry)	$C_{15}H_{26}N_2H_2SO_4$	329.86	v. s.	v. s.
Stannic Chlorid	$SnCl_4$	258.82	..	..
Stannous Chlorid	$SnCl_2 + 2H_2O$	224.22	..	..
Strontium	Sr	86.94	..	..
" Bromid	$SrBr_2 + 6H_2O$	352.94	1.	s.
" Bromid (dry)	$SrBr_2$	245.66	s.	s.
" Carbonate	$SrCO_3$	146.49	..	..
" Iodid	$SrI_2 + 6H_2O$	446.02	0.5	s.
" Iodid (dry)	SrI_2	338.74	s.	s.
" Lactate	$Sr(C_3H_5O_3)_2 + 3H_2O$	317.32	4	s.

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XVII.—Reference Table of Chemic Drugs, their Formulas, Molecular Weight and Solubility.[1]
—*Continued.*

Name.	Symbol or Formula.	Molecular Weight.	Solubility: 1 part dissolves in	
			Water.	Alcohol.
Strontium Lactate (dry)	$Sr(C_3H_5O_3)_2$	263.68	s.	s.
" Nitrate	$Sr(NO_3)_2 + 4H_2O$	......	5	ins.
" Salicylate	$Sr(C_7H_5O_3)_2 + 2H_2O$	394.72	18	66
" Sulphate	$SrSO_4$	182.29	..	..
Strychnin	$C_{21}H_{22}N_2O_2$	331.73	6400	110
" Hydrochlorid	$C_{21}H_{22}N_2O_2.HCl$	367.90	50	s.
" Nitrate	$C_{21}H_{22}N_2O_2HNO_3$	394.30	42	120
" Sulphate	$(C_{21}H_{22}N_2O_2)_2H_2SO_4 + 5H_2O$	850.21	31	65
" Sulphate (dry)	$(C_{21}H_{22}N_2O_2)_2H_2SO_4$	760.81	s.	s.
Sugar (cane-sugar)	$C_{12}H_{22}O_{11}$	339.60	0.46	137.2
" Grape (glucose)	$C_6H_{12}O_6$	178.74	s.	s.
" of Milk (lactose)	$C_{12}H_{22}O_{11} + H_2O$	357.48	4.79	ins.
Sulphonal	$C_7H_{16}S_2O_4$	226.55	360	47
Sulphonethylmethane. See Trional.				
Sulphonmethane. See Sulphonal.				
Sulphur	S	31.83	ins.	ins.
" Dioxid	SO_2	63.59	s.	..
Tantalum	Ta	181.6	..	..
Tartar Emetic. See Antimonyl-Potassium Tartrate.				
Tellurium	Te	126.6	ins.	ins.
Terbium	Tb	158.8	..	..
Terebene	$C_{10}H_{16}$	135.10	sl	3
Terpin Hydrate	$C_{10}H_{18}(OH)_2 + H_2O$	188.74	200	10
Thallium	Tl	202.6	ins.	ins.

Theobromin	$C_7H_8N_4O_2$	......	sp.	s.
Thiosinamin	$CS.N_2H_3(C_3H_5)$	115.33	..	..
Thorium	Th	230.8	..	..
Thulium	Tu	169.7	..	..
Thymol	$C_{10}H_{13}OH$	148.98	1100	<1
" Iodid. See Dithymoldiiodid.				
Tin	Sn	118.1	ins.	ins.
Titanium	Ti	47.7	..	..
Tribromphenol	$C_6H_2Br_3OH$	328.32	ins.	..
Trional	$C_8H_{18}S_2O_4$	240.46	195	v. s.
Tungsten	W	182.6	..	..
Tungstic Oxid	WO_3	......	..	..
Uranium	U	236.7	ins.	ins.
Urea. See Ethyl Carbamate.	$CO(NH_2)_2$	59.65	1	ins.
Urethane	$C_3H_7NO_2$	......	s.	s.
Vanadium	V	50.8	ins.	ins.
Vanillin	$C_8H_8O_3$	150.92	100	s.
Veratrin	$C_{32}H_{52}N_2O_8$	......	1750	2.2
Water	H_2O	17.88	..	..
Xenon	Xe	127.0	..	..
Xylene (xylol)	C_8H_{10}	......	sp.	s.
Ytterbium	Yb	171.7	..	..
Yttrium	Y	88.3	..	..
Zinc	Zn	64.9	ins.	ins.
" Acetate	$Zn(C_2H_3O_2)_2 + 2H_2O$	217.82	2.5	36
" Acetate (dry)	$Zn(C_2H_3O_2)_2$	182.06	s.	s.
" Bromid	$ZnBr_2$	223.62	v. s.	v. s.
" Carbonate (official)	$(ZnCO_3)_2 + 3Zn(OH)_2$	......	ins.	ins.
" Carbonate (pure)	$ZnCO_3$	124.45	ins.	ins.
" Chlorid	$ZnCl_2$	135.26	0.4	v. s.
" Iodid	ZnI_2	316.70	v. s.	v. s.

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

TABLE XVII.—REFERENCE TABLE OF CHEMIC DRUGS, THEIR FORMULAS, MOLECULAR WEIGHT AND SOLUBILITY.[1] —*Continued.*

NAME.	SYMBOL OR FORMULA.	MOLECULAR WEIGHT.	SOLUBILITY: 1 part dissolves in	
			Water.	Alcohol.
Zinc Oxid	ZnO	80.78	ins.	ins.
" Phosphid	Zn_3P_2	256.24	ins.	ins.
" Sulphate	$ZnSO_4 + 7H_2O$	285.41	0.53	ins.
" Sulphate (dry)	$ZnSO_4$	160.25	v. s.	ins.
" Sulphocarbolate	$Zn(C_6H_5SO_4)_2 + 8H_2O$	551.56	1.7	1.7
" Sulphid	ZnS	96.73	ins.	ins.
" Valerianate	$Zn(C_5H_9O_2)_2 + 2H_2O$	301.28	50	35
Zirconium	Zr	89.9	ins.	ins.

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[1] *Abbreviations:* s., soluble; v. s., very soluble; sp., sparingly; a, all proportions; sl., slightly; ins., insoluble; n. ins., nearly insoluble; dec., decomposed.

APPENDIX D.

AVERAGE DOSES, AS GIVEN BY THE U. S. PHARMACOPŒIA, EIGHTH DECENNIAL REVISION.[1]

These doses are given by the Pharmacopœia merely for guidance, and are in no sense compulsory.

PREPARATION.	AVERAGE DOSE.	
	Metric System.[2]	Approximate Equivalent Ordinary System.
Acetanilidum	0.250 Gm.	4 grains.
Acetphenetidinum	0.500 Gm.	7½ grains.
Acetum Opii	0.5 Cc.	8 minims.
Acetum Scillæ	1 Cc.	15 minims.
Acidum Aceticum Dilutum	2 Cc.	30 minims.
Acidum Benzoicum	0.500 Gm.	7½ grains.
Acidum Boricum	0.500 Gm.	7½ grains.
Acidum Camphoricum	1 Gm.	15 grains.
Acidum Citricum	0.500 Gm.	7½ grains.
Acidum Gallicum	1 Gm.	15 grains.
Acidum Hydriodicum Dilutum	0.5 Cc.	8 minims.
Acidum Hydrobromicum Dilutum	4 Cc.	1 fluidrachm.
Acidum Hydrochloricum Dilutum	1 Cc.	15 minims.
Acidum Hydrocyanicum Dilutum	0.1 Cc.	1½ minims.
Acidum Hypophosphorosum Dilutum	0.5 Cc.	8 minims.
Acidum Lacticum	2 Cc.	30 minims.
Acidum Nitricum Dilutum	2 Cc.	30 minims.
Acidum Nitrohydrochloricum	0.2 Cc.	3 minims.
Acidum Nitrohydrochloricum Dilutum	1 Cc.	15 minims.
Acidum Phosphoricum Dilutum	2 Cc.	30 minims.
Acidum Salicylicum	0.500 Gm.	7½ grains.
Acidum Sulphuricum Aromaticum	1 Cc.	15 minims.
Acidum Sulphuricum Dilutum	2 Cc.	30 minims.
Acidum Sulphurosum	2 Cc.	30 minims.
Acidum Tannicum	0.500 Gm.	7½ grains.
Acidum Tartaricum	0.500 Gm.	7½ grains.
Aconitina	0.15 milligramme	1/400 grain.

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[1] Compiled by Reid Hunt and Motter, in Bull. 23, Hygienic Laboratory, U. S. Public Health and Marine Hospital Service.

[2] Doses of 0.030 Gm. and above are given as grams; below, as milligrams.

AVERAGE DOSES, AS GIVEN BY THE U. S. PHARMACOPŒIA, EIGHTH DECENNIAL REVISION.—*Continued.*

PREPARATION.	AVERAGE DOSE.	
	Metric System.	Approximate Equivalent Ordinary System.
Aconitum	0.065 Gm.	1 grain.
Æther	1 Cc.	15 minims.
Æther Aceticus	1 Cc.	15 minims.
Æthylis Carbamas	1 Gm.	15 grains.
Aloe	0.250 Gm.	4 grains.
Aloe Purificata	0.250 Gm.	4 grains.
Aloinum	0.065 Gm.	1 grain.
Alumen	0.500 Gm.	7½ grains.
Ammonii Benzoas	1 Gm.	15 grains.
Ammonii Bromidum	1 Gm.	15 grains.
Ammonii Carbonas	0.250 Gm.	4 grains.
Ammonii Chloridum	0.500 Gm.	7½ grains.
Ammonii Iodidum	0.250 Gm.	4 grains.
Ammonii Salicylas	0.250 Gm.	4 grains.
Ammonii Valeras	0.500 Gm.	7½ grains.
Amylis Nitris	0.2 Cc.	3 minims.
Anisum	0.500 Gm.	7½ grains.
Anthemis	2 Gm.	30 grains.
Antimonii et Potassii Tartras		
Expectorant	5 milligrammes.	1/10 grain.
Emetic	30 milligrammes.	½ grain.
Antipyrina	0.250 Gm.	4 grains.
Apocynum	1 Gm.	15 grains.
Apomorphinæ Hydrochloridum		
Expectorant	2 milligrammes.	1/30 grain.
Emetic	5 milligrammes.	1/10 grain.
Aqua Ammoniæ	1 Cc.	15 minims.
Aqua Amygdalæ Amaræ	4 Cc.	1 fluidrachm.
Aqua Anisi	16 Cc.	4 fluidrachms.
Aqua Aurantii Florum	16 Cc.	4 fluidrachms.
Aqua Aurantii Florum Fortior	8 Cc.	2 fluidrachms.
Aqua Camphoræ	8 Cc.	2 fluidrachms.
Aqua Chloroformi	16 Cc.	4 fluidrachms.
Aqua Cinnamomi	16 Cc.	4 fluidrachms.
Aqua Creosoti	8 Cc.	2 fluidrachms.
Aqua Fœniculi	16 Cc.	4 fluidrachms.
Aqua Hamamelidis	8 Cc.	2 fluidrachms.
Aqua Hydrogenii Dioxidi	4 Cc.	1 fluidrachm.
Aqua Menthæ Piperitæ	16 Cc.	4 fluidrachms.
Aqua Menthæ Viridis	16 Cc.	4 fluidrachms.
Aqua Rosæ	16 Cc.	4 fluidrachms
Aqua Rosæ Fortior	8 Cc.	2 fluidrachms
Argenti Nitras	10 milligrammes.	⅕ grain
Argenti Oxidum	0.065 Gm.	1 grain.
Arnica	1 Gm.	15 grains.

AVERAGE DOSES, AS GIVEN BY THE U. S. PHARMACOPŒIA, EIGHTH DECENNIAL REVISION.— *Continued.*

PREPARATION.	AVERAGE DOSE.	
	Metric System.	Approximate Equivalent Ordinary System.
Arseni Iodidum	5 milligrammes.	1/10 grain.
Arseni Trioxidum	2 milligrammes.	1/30 grain.
Asafœtida	0.250 Gm.	4 grains.
Aspidium	4 Gm.	60 grains.
Atropina	0.4 milligramme.	1/160 grain.
Atropinæ Sulphas	0.4 milligramme.	1/160 grain.
Aurantii Amari Cortex	1 Gm.	15 grains.
Aurantii Dulcis Cortex	1 Gm.	15 grains.
Auri et Sodii Chloridum	5 milligrammes	1/10 grain.
Balsamum Peruvianum	1 Gm.	15 grains.
Balsamum Tolutanum	1 Gm.	15 grains.
Belladonnæ Folia	0.065 Gm.	1 grain.
Belladonnæ Radix	0.045 Gm.	¾ grain.
Benzaldehydum	0.03 Cc.	½ minim.
Benzoinum	1 Gm.	15 grains.
Benzosulphinidum	0.200 Gm.	3 grains.
Berberis	2 Gm.	30 grains.
Betanaphthol	0.250 Gm.	4 grains.
Bismuthi Citras	0.125 Gm.	2 grains.
Bismuthi et Ammonii Citras	0.125 Gm.	2 grains.
Bismuthi Subcarbonas	0.500 Gm.	7½ grains.
Bismuthi Subgallas	0.250 Gm.	4 grains.
Bismuthi Subnitras	0.500 Gm.	7½ grains.
Bismuthi Subsalicylas	0.250 Gm.	4 grains.
Bromoformum	0.2 Cc.	3 minims.
Buchu	2 Gm.	30 grains.
Caffeina	0.065 Gm.	1 grain.
Caffeina Citrata	0.125 Gm.	2 grains.
Caffeina Citrata Effervescens	4 Gm.	60 grains.
Calamus	1 Gm.	15 grains.
Calcii Bromidum	1 Gm.	15 grains.
Calcii Carbonas Præcipitatus	1 Gm.	15 grains.
Calcii Chloridum	0.500 Gm.	7½ grains.
Calcii Hypophosphis	0.500 Gm.	7½ grains.
Calcii Phosphas Præcipitatus	1 Gm.	15 grains.
Calendula	1 Gm.	15 grains.
Calumba	2 Gm.	30 grains.
Calx Chlorinata	0.250 Gm.	4 grains.
Calx Sulphurata	0.065 Gm.	1 grain.
Cambogia	0.125 Gm.	2 grains.
Camphora	0.125 Gm.	2 grains.
Camphora Monobromata	0.125 Gm.	2 grains.
Cannabis Indica	0.065 Gm.	1 grain.
Cantharis	0.030 Gm.	½ grain.
Capsicum	0.065 Gm.	1 grain.

AVERAGE DOSES, AS GIVEN BY THE U. S. PHARMACOPŒIA, EIGHTH DECENNIAL REVISION.—*Continued.*

PREPARATION.	AVERAGE DOSE.	
	Metric System.	Approximate Equivalent Ordinary System.
Carbo Ligni	1 Gm.	15 grains.
Cardamomum	1 Gm.	15 grains.
Carum	1 Gm.	15 grains.
Caryophyllus	0.250 Gm.	4 grains.
Cassia Fistula	4 Gm.	60 grains.
Cerii Oxalas	0.065 Gm.	1 grain.
Chimaphila	2 Gm.	30 grains.
Chirata	1 Gm.	15 grains.
Chloralformamidum	1 Gm.	15 grains.
Chloralum Hydratum	1 Gm.	15 grains.
Chloroformum	0.3 Cc.	5 minims.
Chondrus ....In decoction	15 Gm.	4 drachms.
Chrysarobinum	0.030 Gm.	½ grain.
Cimicifuga	1 Gm.	15 grains.
Cinchona	1 Gm.	15 grains.
Cinchona Rubra	1 Gm.	15 grains.
Cinchonidinæ Sulphas	0.250 Gm.	4 grains.
Cinchoninæ Sulphas	0.250 Gm.	4 grains.
Cinnaldehydum	0.05 Cc.	1 minim.
Cinnamomum Saigonicum	0.250 Gm.	4 grains.
Cinnamomum Zeylanicum	0.250 Gm.	4 grains.
Coca	2 Gm.	30 grains.
Cocaina	0.030 Gm.	½ grain.
Cocainæ Hydrochloridum	0.030 Gm.	½ grain.
Codeina	0.030 Gm.	½ grain.
Codeinæ Phosphas	0.030 Gm.	½ grain.
Codeinæ Sulphas	0.030 Gm.	½ grain.
Colchici Cormus	0.250 Gm.	4 grains.
Colchici Semen	0.200 Gm.	3 grains.
Colchicina	0.5 milligramme.	1/128 grain.
Colocynthis	0.065 Gm.	1 grain.
Confectio Sennæ	4 Gm.	60 grains.
Conium	0.200 Gm.	3 grains.
Convallaria	0.500 Gm.	7½ grains.
Copaiba	1 Cc.	15 minims.
Coriandrum	0.500 Gm.	7½ grains.
Creosotum	0.2 Cc.	3 minims.
Cresol	0.05 Cc.	1 minim.
Creta Præparata	1 Gm.	15 grains.
Cubeba	1 Gm.	15 grains.
Cupri Sulphas ... { Astringent ..	10 milligrammes.	⅕ grain.
Cupri Sulphas ... { Emetic	0.250 Gm.	4 grains.
Cusso	16 Gm.	240 grains.
Cypripedium	1 Gm.	5 grains.
Digitalis	0.065 Gm.	1 grain.
Elaterinum	5 milligrammes.	1/10 grain.

AVERAGE DOSES, AS GIVEN BY THE U. S. PHARMACOPŒIA, EIGHTH DECENNIAL REVISION.—*Continued.*

PREPARATION.	AVERAGE DOSE.	
	Metric System.	Approximate Equivalent Ordinary System.
Elixir Ferri, Quininæ, et Strychninæ Phosphatum	4 Cc.	1 fluidrachm.
Emulsum Amygdalæ	120 Cc.	4 fluidounces.
Emulsum Asafœtidæ	16 Cc.	4 fluidrachms
Emulsum Chloroformi	8 Cc.	2 fluidrachms
Emulsum Olei Morrhuæ	8 Cc.	2 fluidrachms.
Emulsum Olei Morrhuæ cum Hypophosphitibus	8 Cc.	2 fluidrachms
Emulsum Olei Terebinthinæ	4 Cc.	1 fluidrachm.
Ergota	2 Gm.	30 grains.
Eriodictyon	1 Gm.	15 grains.
Eucalyptol	0.3 Cc.	5 minims.
Eucalyptus	2 Gm.	30 grains.
Eugenol	0.2 Cc.	3 minims.
Euonymus	0.500 Gm.	7½ grains.
Eupatorium	2 Gm.	30 grains.
Extractum Aloes	0.125 Gm.	2 grains.
Extractum Belladonnæ Foliorum	10 milligrammes.	⅕ grain.
Extractum Cannabis Indicæ	10 milligrammes.	⅕ grain.
Extractum Cimicifugæ	0.250 Gm.	4 grains.
Extractum Colchici Cormi	0.065 Gm.	1 grain.
Extractum Colocynthidis	0.030 Gm.	½ grain.
Extractum Colocynthidis Compositum	0.500 Gm.	7½ grains.
Extractum Digitalis	10 milligrammes.	⅕ grain.
Extractum Ergotæ	0.250 Gm.	4 grains.
Extractum Euonymi	0.125 Gm.	2 grains.
Extractum Gentianæ	0.250 Gm.	4 grains.
Extractum Glycyrrhizæ	1 Gm.	15 grains.
Extractum Glycyrrhizæ Purum	1 Gm.	15 grains.
Extractum Hæmatoxyli	1 Gm.	15 grains.
Extractum Hyoscyami	0.065 Gm.	1 grain.
Extractum Krameriæ	0.500 Gm.	7½ grains.
Extractum Leptandræ	0.250 Gm.	4 grains.
Extractum Malti	16 Cc.	4 fluidrachms
Extractum Nucis Vomicæ	15 milligrammes.	¼ grain.
Extractum Opii	0.030 Gm.	½ grain.
Extractum Physostigmatis	8 milligrammes.	⅛ grain.
Extractum Quassiæ	0.065 Gm.	1 grain.
Extractum Rhamni Purshianæ	0.250 Gm.	4 grains.
Extractum Rhei	0.250 Gm.	4 grains.
Extractum Scopolæ	10 milligrammes.	⅕ grain.
Extractum Stramonii	10 milligrammes.	⅕ grain.
Extractum Sumbul	0.250 Gm.	4 grains.
Extractum Taraxaci	1 Gm.	15 grains.

AVERAGE DOSES, AS GIVEN BY THE U. S. PHARMACOPŒIA, EIGHTH DECENNIAL REVISION.—*Continued.*

PREPARATION.	AVERAGE DOSE.	
	Metric System.	Approximate Equivalent Ordinary System.
Fel Bovis Purificatum	0.500 Gm.	7½ grains.
Ferri Carbonas Saccharatus	0.250 Gm.	4 grains.
Ferri Chloridum	0.065 Gm.	1 grain.
Ferri Citras	0.250 Gm.	4 grains.
Ferri et Ammonii Citras	0.250 Gm.	4 grains.
Ferri et Ammonii Sulphas	0.500 Gm.	7½ grains.
Ferri et Ammonii Tartras	0.250 Gm.	4 grains.
Ferri et Potassii Tartras	0.250 Gm.	4 grains.
Ferri et Quininæ Citras	0.250 Gm.	4 grains.
Ferri et Quininæ Citras Solubilis	0.250 Gm.	4 grains.
Ferri et Strychninæ Citras	0.125 Gm.	2 grains.
Ferri Hydroxidum cum Magnesii Oxido..Arsenical antidote	120 Cc.	4 fluidouncs.
Ferri Hypophosphis	0.200 Gm.	3 grains.
Ferri Phosphas Solubilis	0.250 Gm.	4 grains.
Ferri Pyrophosphas Solubilis	0.250 Gm.	4 grains.
Ferri Sulphas	0.200 Gm.	3 grains.
Ferri Sulphas Exsiccatus	0.125 Gm.	2 grains.
Ferri Sulphas Granulatus	0.200 Gm.	3 grains.
Ferrum Reductum	0.065 Gm.	1 grain.
Fluidextractum Aconiti	0.05 Cc.	1 minim.
Fluidextractum Apocyni	1 Cc.	15 minims.
Fluidextractum Aromaticum	1 Cc.	15 minims.
Fluidextractum Aurantii Amari	1 Cc.	15 minims.
Fluidextractum Belladonnæ Radicis	0.05 Cc.	1 minim.
Fluidextractum Berberidis	2 Cc.	30 minims.
Fluidextractum Buchu	2 Cc.	30 minims.
Fluidextractum Calami	1 Cc.	15 minims.
Fluidextractum Calumbæ	2 Cc.	30 minims.
Fluidextractum Cannabis Indicæ	0.05 Cc.	1 minim.
Fluidextractum Capsici	0.05 Cc.	1 minim.
Fluidextractum Chimaphilæ	2 Cc.	30 minims.
Fluidextractum Chiratæ	1 Cc.	15 minims.
Fluidextractum Cimicifugæ	1 Cc.	15 minims.
Fluidextractum Cinchonæ	1 Cc.	15 minims.
Fluidextractum Cocæ	2 Cc.	30 minims.
Fluidextractum Colchici Seminis	0.2 Cc.	3 minims.
Fluidextractum Conii	0.2 Cc.	3 minims.
Fluidextractum Convallariæ	0.5 Cc.	8 minims.
Fluidextractum Cubebæ	1 Cc.	15 minims.
Fluidextractum Cypripedii	1 Cc.	15 minims.
Fluidextractum Digitalis	0.05 Cc.	1 minim.
Fluidextractum Ergotæ	2 Cc.	30 minims.
Fluidextractum Eriodictyi	1 Cc.	15 minims.
Fluidextractum Eucalypti	2 Cc.	30 minims.

Average Doses, as Given by the U. S. Pharmacopœia, Eighth Decennial Revision.—*Continued.*

Preparation.	Average Dose.	
	Metric System.	Approximate Equivalent Ordinary System.
Fluidextractum Euonymi	0.5 Cc.	8 minims.
Fluidextractum Eupatorii	2 Cc.	30 minims.
Fluidextractum Frangulæ	1 Cc.	15 minims.
Fluidextractum Gelsemii	0.05 Cc.	1 minim.
Fluidextractum Gentianæ	1 Cc.	15 minims.
Fluidextractum Geranii	1 Cc.	15 minims.
Fluidextractum Glycyrrhizæ	2 Cc.	30 minims.
Fluidextractum Granati	2 Cc.	30 minims.
Fluidextractum Grindeliæ	2 Cc.	30 minims.
Fluidextractum Guaranæ	2 Cc.	30 minims.
Fluidextractum Hamamelidis Foliorum	2 Cc.	30 minims.
Fluidextractum Hydrastis	2 Cc.	30 minims.
Fluidextractum Hyoscyami	0.2 Cc.	3 minims.
Fluidextractum Ipecacuanhæ { Emetic	1 Cc.	15 minims.
Fluidextractum Ipecacuanhæ { Expectorant	0.05 Cc.	1 minim.
Fluidextractum Krameriæ	1 Cc.	15 minims.
Fluidextractum Lappæ	2 Cc.	30 minims.
Fluidextractum Leptandræ	1 Cc.	15 minims.
Fluidextractum Lobeliæ	0.5 Cc.	8 minims.
Fluidextractum Lupulini	0.5 Cc.	8 minims.
Fluidextractum Matico	4 Cc.	1 fluidrachm.
Fluidextractum Nucis Vomicæ	0.05 Cc.	1 minim.
Fluidextractum Pareiræ	2 Cc.	30 minims.
Fluidextractum Phytolaccæ { Emetic	1 Cc.	15 minims.
Fluidextractum Phytolaccæ { Alterative	0.1 Cc.	1½ minims.
Fluidextractum Pilocarpi	2 Cc.	30 minims.
Fluidextractum Podophylli	0.5 Cc.	8 minims.
Fluidextractum Pruni Virginianæ	2 Cc.	30 minims.
Fluidextractum Quassiæ	0.5 Cc.	8 minims.
Fluidextractum Quercus	1 Cc.	15 minims.
Fluidextractum Quillajæ	0.2 Cc.	3 minims.
Fluidextractum Rhamni Purshianæ	1 Cc.	15 minims.
Fluidextractum Rhamni Purshianæ Aromaticum	1 Cc.	15 minims.
Fluidextractum Rhei	1 Cc.	15 minims.
Fluidextractum Rhois Glabræ	1 Cc.	15 minims.
Fluidextractum Rosæ	2 Cc.	30 minims.
Fluidextractum Rubi	1 Cc.	15 minims.
Fluidextractum Sabinæ	0.3 Cc.	5 minims.
Fluidextractum Sanguinariæ	0.1 Cc.	1½ minims.
Fluidextractum Sarsaparillæ	2 Cc.	30 minims.
Fluidextractum Sarsaparillæ Compositum	2 Cc.	30 minims.
Fluidextractum Scillæ	0.1 Cc.	1½ minims.
Fluidextractum Scopolæ	0.05 Cc.	1 minim.

AVERAGE DOSES, AS GIVEN BY THE U. S. PHARMACOPŒIA, EIGHTH DECENNIAL REVISION.—*Continued.*

PREPARATION.	AVERAGE DOSE.	
	Metric System.	Approximate Equivalent Ordinary System.
Fluidextractum Scutellariæ	1 Cc.	15 minims.
Fluidextractum Senegæ	1 Cc.	15 minims.
Fluidextractum Sennæ	2 Cc.	30 minims.
Fluidextractum Serpentariæ	1 Cc.	15 minims.
Fluidextractum Spigeliæ	4 Cc.	1 fluidrachm.
Fluidextractum Staphisagriæ	0.05 Cc.	1 minim.
Fluidextractum Stillingiæ	2 Cc.	30 minims.
Fluidextractum Stramonii	0.05 Cc.	1 minim.
Fluidextractum Sumbul	2 Cc.	30 minims.
Fluidextractum Taraxaci	8 Cc.	2 fluidrachms
Fluidextractum Tritici	8 Cc.	2 fluidrachms
Fluidextractum Uvæ Ursi	2 Cc.	30 minims.
Fluidextractum Valerianæ	2 Cc.	30 minims.
Fluidextractum Veratri	0.1 Cc.	1½ minims.
Fluidextractum Viburni Opuli	2 Cc.	30 minims.
Fluidextractum Viburni Prunifolii	2 Cc.	30 minims.
Fluidextractum Xanthoxyli	2 Cc.	30 minims.
Fluidextractum Zingiberis	1 Cc.	15 minims.
Fœniculum	1 Gm.	15 grains.
Frangula	1 Gm.	15 grains.
Galla	0.500 Gm.	7½ grains.
Gambir	1 Gm.	15 grains.
Gelsemium	0.065 Gm.	1 grain.
Gentiana	1 Gm.	15 grains.
Geranium	1 Gm.	15 grains.
Glandulæ Suprarenales Siccæ	0.250 Gm.	4 grains.
Glandulæ Thyroideæ Siccæ	0.250 Gm.	4 grains.
Glycerinum	4 Cc.	1 fluidrachm.
Glyceritum Acidi Tannici	2 Cc.	30 minims.
Glyceritum Ferri, Quininæ, et Strychninæ Phosphatum	1 Cc.	15 minims.
Glyceritum Hydrastis	2 Cc.	30 minims.
Glyceritum Phenolis	0.3 Cc.	5 minims.
Glycyrrhiza	2 Gm.	30 grains.
Glycyrrhizinum Ammoniatum	0.250 Gm.	4 grains.
Gossypii Cortex	2 Gm.	30 grains.
Granatum	2 Gm.	30 grains.
Grindelia	2 Gm.	30 grains.
Guaiacol	0.5 Cc.	8 minims.
Guaiacolis Carbonas	1 Gm.	15 grains.
Guaiacum	1 Gm.	15 grains.
Guarana	2 Gm.	30 grains.
Hamamelidis Cortex	2 Gm.	30 grains.
Hamamelidis Folia	2 Gm.	30 grains.
Hedeoma	8 Gm.	120 grains.
Hexamethylenamina	0.250 Gm.	4 grains.

AVERAGE DOSES, AS GIVEN BY THE U. S. PHARMACOPŒIA, EIGHTH DECENNIAL REVISION.—*Continued.*

PREPARATION.	AVERAGE DOSE.	
	Metric System.	Approximate Equivalent Ordinary System.
Homatropinæ Hydrobromidum	0.5 milligramme.	1/128 grain.
Humulus	2 Gm.	30 grains.
Hydrargyri Chloridium Corrosivum	3 milligrammes.	1/20 grain.
Hydrargyri Chloridum Mite: Laxative	0.125 Gm.	2 grains.
Hydrargyri Chloridum Mite: Alterative	0.065 Gm.	1 grain.
Hydrargyri Iodidum Flavum	10 milligrammes.	1/5 grain.
Hydrargyri Iodidum Rubrum	3 milligrammes.	1/20 grain.
Hydrargyrum cum Creta	0.250 Gm.	4 grains.
Hydrastina	10 milligrammes.	1/5 grain.
Hydrastininæ Hydrochloridum	0.030 Gm.	1/2 grain.
Hydrastis	2 Gm.	30 grains.
Hyoscinæ Hydrobromidum	0.5 milligramme.	1/128 grain.
Hyoscyaminæ Hydrobromidum	0.5 milligramme.	1/128 grain.
Hyoscyaminæ Sulphas	0.5 milligramme.	1/128 grain.
Hyoscyamus	0.250 Gm.	4 grains.
Infusum Digitalis	8 Cc.	2 fluidrachms.
Infusum Pruni Virginianæ	60 Cc.	2 fluidounces
Infusum Sennæ Compositum	120 Cc.	4 fluidounces.
Iodoformum	0.250 Gm.	4 grains.
Iodolum	0.250 Gm.	4 grains.
Iodum	5 milligrammes.	1/10 grain.
Ipecacuanha: Expectorant	0.065 Gm.	1 grain.
Ipecacuanha: Emetic	1 Gm.	15 grains.
Jalapa	1 Gm.	15 grains.
Kino	0.500 Gm.	7 1/2 grains.
Krameria	1 Gm.	15 grains.
Lactucarium	1 Gm.	15 grains.
Lappa	2 Gm.	30 grains.
Leptandra	1 Gm.	15 grains.
Limonis Succus	30 Cc.	1 fluidounce.
Liquor Acidi Arsenosi	0.2 Cc.	3 minims.
Liquor Ammonii Acetatis	16 Cc.	4 fluidrachms
Liquor Antisepticus	4 Cc.	1 fluidrachm.
Liquor Arseni et Hydrargyri Iodidi	0.1 Cc.	1 1/2 minims.
Liquor Calcis	16 Cc.	4 fluidrachms
Liquor Chlori Compositus	4 Cc.	1 fluidrachm.
Liquor Ferri Chloridi	0.1 Cc.	1 1/2 minims.
Liquor Ferri et Ammonii Acetatis	16 Cc.	4 fluidrachms.
Liquor Ferri Subsulphatis	0.2 Cc.	3 minims.
Liquor Iodi Compositus	0.2 Cc.	3 minims.
Liquor Magnesii Citratis	360 Cc.	12 fluidounces.
Liquor Potassii Arsenitis	0.2 Cc.	3 minims.

AVERAGE DOSES, AS GIVEN BY THE U. S. PHARMACOPŒIA, EIGHTH DECENNIAL REVISION.—*Continued.*

PREPARATION.	AVERAGE DOSE.	
	Metric System.	Approximate Equivalent Ordinary System.
Liquor Potassii Citratis	16 Cc.	4 fluidrachms
Liquor Potassii Hydroxidi	1 Cc.	15 minims.
Liquor Sodæ Chlorinatæ	1 Cc.	15 minims.
Liquor Sodii Arsenatis	0.2 Cc.	3 minims.
Liquor Sodii Hydroxidi	1 Cc.	15 minims.
Liquor Sodii Phosphatis Compositus	8 Cc.	2 fluidrachms
Lithii Benzoas	1 Gm.	15 grains.
Lithii Bromidum	1 Gm.	15 grains.
Lithii Carbonas	0.500 Gm.	7½ grains.
Lithii Citras	0.500 Gm.	7½ grains.
Lithii Citras Effervescens	8 Gm.	120 grains.
Lithii Salicylas	1 Gm.	15 grains.
Lobelia	0.500 Gm.	7½ grains.
Lupulinum	0.500 Gm.	7½ grains.
Magnesii Carbonas	3 Gm.	45 grains.
Magnesii Oxidum	2 Gm.	30 grains.
Magnesii Oxidum Ponderosum	2 Gm.	30 grains.
Magnesii Sulphas	16 Gm.	240 grains.
Magnesii Sulphas Effervescens	16 Gm.	240 grains.
Mangani Dioxidum Præcipitatum	0.250 Gm.	4 grains.
Mangani Hypophosphis	0.200 Gm.	3 grains.
Mangani Sulphas	0.250 Gm.	4 grains.
Manna	16 Gm.	240 grains.
Marrubium	2 Gm.	30 grains.
Massa Ferri Carbonatis	0.250 Gm.	4 grains.
Massa Hydrargyri	0.250 Gm.	4 grains.
Mastiche	2 Gm.	30 grains.
Matico	4 Gm.	60 grains.
Matricaria	16 Gm.	240 grains.
Mel	4 Cc.	1 fluidrachm.
Mel Depuratum	4 Cc.	1 fluidrachm.
Mel Rosæ	4 Cc.	1 fluidrachm.
Mentha Piperita	4 Gm.	60 grains.
Mentha Viridis	4 Gm.	60 grains.
Menthol	0.065 Gm.	1 grain.
Methylis Salicylas	1 Cc.	15 minims.
Methylthioninæ Hydrochloridum	0.250 Gm.	4 grains.
Mezereum	0.500 Gm.	7½ grains.
Mistura Cretæ	16 Cc.	4 fluidrachms
Mistura Ferri Composita	16 Cc.	4 fluidrachms
Mistura Glycyrrhizæ Composita	8 Cc.	2 fluidrachms
Mistura Rhei et Sodæ	4 Cc.	1 fluidrachm.
Morphina	10 milligrammes.	⅙ grain.
Morphinæ Acetas	15 milligrammes.	¼ grain.

AVERAGE DOSES, AS GIVEN BY THE U. S. PHARMACOPŒIA, EIGHTH DECENNIAL REVISION.—*Continued.*

PREPARATION.	AVERAGE DOSE.	
	Metric System.	Approximate Equivalent Ordinary System.
Morphinæ Hydrochloridum	15 milligrammes.	¼ grain.
Morphinæ Sulphas	15 milligrammes.	¼ grain.
Moschus	0.250 Gm.	4 grains.
Mucilago Acaciæ	16 Cc.	4 fluidrachms
Mucilago Sassafras Medullæ	16 Cc.	4 fluidrachms
Mucilago Tragacanthæ	16 Cc.	4 fluidrachms
Mucilago Ulmi	16 Cc.	4 fluidrachms
Myristica	0.500 Gm.	7½ grains.
Myrrha	0.500 Gm.	7½ grains.
Naphthalenum	0.125 Gm.	2 grains.
Nux Vomica	0.065 Gm.	1 grain.
Oleoresina Aspidii	2 Gm.	30 grains.
Oleoresina Capsici	0.030 Gm.	½ grain.
Oleoresina Cubebæ	0.500 Gm.	7½ grains.
Oleoresina Lupulini	0.200 Gm.	3 grains.
Oleoresina Piperis	0.030 Gm.	½ grain.
Oleoresina Zingiberis	0.030 Gm.	½ grain.
Oleum Amygdalæ Amaræ	0.03 Cc.	½ minim.
Oleum Amygdalæ Expressum	30 Cc.	1 fluidounce.
Oleum Anisi	0.2 Cc.	3 minims.
Oleum Aurantii Corticis	0.2 Cc.	3 minims.
Oleum Betulæ	1 Cc.	15 minims.
Oleum Cajuputi	0.5 Cc.	8 minims.
Oleum Cari	0.2 Cc.	3 minims.
Oleum Caryophylli	0.2 Cc.	3 minims.
Oleum Chenopodii	0.2 Cc.	3 minims.
Oleum Cinnamomi	0.05 Cc.	1 minim.
Oleum Copaibæ	0.5 Cc.	8 minims.
Oleum Coriandri	0.2 Cc.	3 minims.
Oleum Cubebæ	0.5 Cc.	8 minims.
Oleum Erigerontis	1 Cc.	15 minims.
Oleum Eucalypti	0.5 Cc.	8 minims.
Oleum Fœniculi	0.2 Cc.	3 minims.
Oleum Gaultheriæ	1 Cc.	15 minims.
Oleum Gossypii Seminis	16 Cc.	4 fluidrachms
Oleum Hedeomæ	0.2 Cc.	3 minims.
Oleum Juniperi	0.2 Cc.	3 minims.
Oleum Lavandulæ Florum	0.2 Cc.	3 minims.
Oleum Limonis	0.2 Cc.	3 minims.
Oleum Lini	30 Cc.	1 fluidounce.
Oleum Menthæ Piperitæ	0.2 Cc.	3 minims.
Oleum Menthæ Viridis	0.2 Cc.	3 minims.
Oleum Morrhuæ	16 Cc.	4 fluidrachms
Oleum Myristicæ	0.2 Cc.	3 minims.
Oleum Olivæ	30 Cc.	1 fluidounce.
Oleum Picis Liquidæ	0.2 Cc.	3 minims.
Oleum Pimentæ	0.2 Cc.	3 minims.

AVERAGE DOSES, AS GIVEN BY THE U. S. PHARMACOPŒIA, EIGHTH DECENNIAL REVISION.—*Continued.*

PREPARATION.	AVERAGE DOSE.	
	Metric System.	Approximate Equivalent Ordinary System.
Oleum Ricini	16 Cc.	4 fluidrachms
Oleum Rosmarini	0.2 Cc.	3 minims.
Oleum Sabinæ	0.05 Cc.	1 minim.
Oleum Santali	0.5 Cc.	8 minims.
Oleum Sassafras	0.2 Cc.	3 minims.
Oleum Sinapis Volatile	0.008 Cc.	⅛ minim.
Oleum Terebinthinæ Rectificatum	1 Cc.	15 minims.
Oleum Thymi	0.2 Cc.	3 minims.
Oleum Tiglii	0.05 Cc.	1 minim.
Opii Pulvis	0.065 Gm.	1 grain.
Opium	0.100 Gm.	1½ grains.
Opium Deodoratum	0.065 Gm.	1 grain.
Opium Granulatum	0.065 Gm.	1 grain.
Pancreatinum	0.500 Gm.	7½ grains.
Paraldehydum	2 Cc.	30 minims.
Pareira	2 Gm.	30 grains.
Pelletierinæ Tannas	0.250 Gm.	4 grains.
Pepo	30 Gm.	1 ounce.
Pepsinum	0.250 Gm.	4 grains.
Phenol	0.065 Gm.	1 grain.
Phenol Liquefactum	0.05 Cc.	1 minim.
Phenylis Salicylas	0.500 Gm.	7½ grains.
Phosphorus	0.5 milligramme.	1/128 grain.
Physostigma	0.100 Gm.	1½ grains.
Physostigminæ Salicylas	1 milligramme.	1/64 grain.
Physostigminæ Sulphas	1 milligramme.	1/64 grain.
Phytolacca { Emetic	1 Gm.	15 grains.
Alterative	0.125 Gm.	2 grains.
Pilocarpinæ Hydrochloridum	10 milligrammes.	⅙ grain.
Pilocarpinæ Nitras	10 milligrammes.	⅙ grain.
Pilocarpus	2 Gm.	30 grains.
Pilulæ Aloes	2 pills.	
Pilulæ Aloes et Ferri	2 pills.	
Pilulæ Aloes et Masticħes	2 pills.	
Pilulæ Aloes et Myrrhæ	2 pills.	
Pilulæ Asafœtidæ	2 pills.	
Pilulæ Catharticæ Compositæ	2 pills.	
Pilulæ Catharticæ Vegetabiles	2 pills.	
Pilulæ Ferri Carbonatis	2 pills.	
Pilulæ Ferri Iodidi	2 pills.	
Pilulæ Laxativæ Compositæ	2 pills.	
Pilulæ Opii	1 pill.	
Pilulæ Phosphori	1 pill.	
Pilulæ Podophylli, Belladonnæ et Capsici	1 pill.	
Pilulæ Rhei Compositæ	2 pills.	

AVERAGE DOSES, AS GIVEN BY THE U. S. PHARMACOPŒIA, EIGHTH DECENNIAL REVISION.—*Continued.*

PREPARATION.	AVERAGE DOSE.	
	Metric System.	Approximate Equivalent Ordinary System.
Pimenta	1 Gm.	15 grains.
Piper	0.500 Gm.	7½ grains.
Piperina	0.200 Gm.	3 grains.
Pix Liquida	0.500 Gm.	7½ grains.
Plumbi Acetas	0.065 Gm.	1 grain.
Podophyllum	0.500 Gm.	7½ grains.
Potassii Acetas	2 Gm.	30 grains.
Potassii Bicarbonas	2 Gm.	30 grains.
Potassii Bitartras	2 Gm.	30 grains.
Potassii Bromidum	1 Gm.	15 grains.
Potassii Carbonas	1 Gm.	15 grains.
Potassii Chloras	0.250 Gm.	4 grains.
Potassii Citras	1 Gm.	15 grains.
Potassii Citras Effervescens	4 Gm.	60 grains.
Potassii Cyanidum	10 milligrammes.	⅕ grain.
Potassii Dichromas	10 milligrammes.	⅕ grain.
Potassii et Sodii Tartras	8 Gm.	120 grains.
Potassii Ferrocyanidum	0.500 Gm.	7½ grains.
Potassii Hypophosphis	0.500 Gm.	7½ grains.
Potassii Iodidum	0.500 Gm.	7½ grains.
Potassii Nitras	0.500 Gm.	7½ grains.
Potassii Permanganas	0.065 Gm.	1 grain.
Potassii Sulphas	2 Gm.	30 grains.
Prunus Virginiana	2 Gm.	30 grains.
Pulvis Acetanilidi Compositus	0.500 Gm.	7½ grains.
Pulvis Aromaticus	1 Gm.	15 grains.
Pulvis Cretæ Compositus	2 Gm.	30 grains.
Pulvis Effervescens Compositus	1 set of 2 powders.	
Pulvis Glycyrrhizæ Compositus	4 Gm.	60 grains.
Pulvis Ipecacuanhæ et Opii	0.500 Gm.	7½ grains.
Pulvis Jalapæ Compositus	2 Gm.	30 grains.
Pulvis Morphinæ Compositus	0.500 Gm.	7½ grains.
Pulvis Rhei Compositus	2 Gm.	30 grains.
Pyrethrum	2 Gm.	30 grains.
Quassia	0.500 Gm.	7½ grains.
Quercus	1 Gm.	15 grains.
Quinina	0.250 Gm.	4 grains.
Quininæ Bisulphas	0.250 Gm.	4 grains.
Quininæ Hydrobromidum	0.250 Gm.	4 grains.
Quininæ Hydrochloridum	0.250 Gm.	4 grains.
Quininæ Salicylas	0.250 Gm.	4 grains.
Quininæ Sulphas	0.250 Gm.	4 grains.
Resina	0.250 Gm.	4 grains.
Resina Jalapæ	0.125 Gm.	2 grains.

AVERAGE DOSES, AS GIVEN BY THE U. S. PHARMACOPŒIA, EIGHTH DECENNIAL REVISION.—*Continued.*

PREPARATION.	AVERAGE DOSE.	
	Metric System.	Approximate Equivalent Ordinary System.
Resina Podophylli { Purgative ..	15 milligrammes.	¼ grain.
Resina Podophylli { Laxative ...	5 milligrammes.	1/10 grain.
Resina Scammonii	0.200 Gm.	3 grains.
Resorcinol	0.125 Gm.	2 grains.
Rhamnus Purshiana	1 Gm.	15 grains.
Rheum	1 Gm.	15 grains.
Rhus Glabra	1 Gm.	15 grains.
Rubus	1 Gm.	15 grains.
Sabal	1 Gm.	15 grains.
Sabina	0.500 Gm.	7½ grains.
Safrolum	0.3 Cc.	5 minims.
Salicinum	1 Gm.	15 grains.
Salvia	2 Gm.	30 grains.
Sanguinaria	0.125 Gm.	2 grains.
Santoninum	0.065 Gm.	1 grain.
Sarsaparilla	2 Gm.	30 grains.
Sassafras	8 Gm.	120 grains.
Scammonium	0.250 Gm.	4 grains.
Scilla	0.125 Gm.	2 grains.
Scoparius	1 Gm.	15 grains.
Scopola	0.045 Gm.	¾ grain.
Scopolaminæ Hydrobromidum ..	0.5 milligramme.	1/120 grain.
Scutellaria	1 Gm.	15 grains.
Senega	1 Gm.	15 grains.
Senna	4 Gm.	60 grains.
Serpentaria	1 Gm.	15 grains.
Serum Antidiphthericum Immunizing dose for well persons.		3,000 units. 500 units.
Sinapis Alba ....Emetic..	8 Gm.	120 grains.
Sinapis Nigra ....Emetic..	8 Gm.	120 grains.
Sodii Acetas	1 Gm.	15 grains.
Sodii Arsenas	5 milligrammes.	1/10 grain.
Sodii Arsenas Exsiccatus	3 milligrammes.	1/20 grain.
Sodii Benzoas	1 Gm.	15 grains.
Sodii Bicarbonas	1 Gm.	15 grains.
Sodii Bisulphis	0.500 Gm.	7½ grains.
Sodii Boras	0.500 Gm.	7½ grains.
Sodii Bromidum	1 Gm.	15 grains.
Sodii Carbonas Monohydratus ..	0.250 Gm.	4 grains.
Sodii Chloras	0.250 Gm.	4 grains.
Sodii Chloridum ....Emetic..	16 Gm.	240 grains.
Sodii Citras	1 Gm.	15 grains.
Sodii Hypophosphis	1 Gm.	15 grains.
Sodii Iodidum	0.500 Gm.	7½ grains.
Sodii Nitras	1 Gm.	15 grains.

AVERAGE DOSES, AS GIVEN BY THE U. S. PHARMACOPŒIA, EIGHTH DECENNIAL REVISION.—*Continued.*

PREPARATION.	AVERAGE DOSE.	
	Metric System.	Approximate Equivalent Ordinary System.
Sodii Nitris	0.065 Gm.	1 grain.
Sodii Phenolsulphonas	0.250 Gm.	4 grains.
Sodii Phosphas	2 Gm.	30 grains.
Sodii Phosphas Effervescens	8 Gm.	120 grains.
Sodii Phosphas Exsiccatus	1 Gm.	15 grains.
Sodii Pyrophosphas	2 Gm.	30 grains.
Sodii Salicylas	1 Gm.	15 grains.
Sodii Sulphas	16 Gm.	240 grains.
Sodii Sulphis	1 Gm.	15 grains.
Sodii Thiosulphas	1 Gm.	15 grains.
Sparteinæ Sulphas	10 milligrammes.	⅙ grain.
Spigelia	4 Gm.	60 grains.
Spiritus Ætheris	4 Cc.	1 fluidrachm
Spiritus Ætheris Compositus	4 Cc.	1 fluidrachm
Spiritus Ætheris Nitrosi	2 Cc.	30 minims.
Spiritus Ammoniæ	1 Cc.	15 minims.
Spiritus Ammoniæ Aromaticus	2 Cc.	30 minims.
Spiritus Amygdalæ Amaræ	0.5 Cc.	8 minims.
Spiritus Anisi	4 Cc.	1 fluidrachm
Spiritus Camphoræ	1 Cc.	15 minims.
Spiritus Chloroformi	2 Cc.	30 minims.
Spiritus Cinnamomi	2 Cc.	30 minims.
Spiritus Gaultheriæ	2 Cc.	30 minims.
Spiritus Glycerylis Nitratis	0.05 Cc.	1 minim.
Spiritus Juniperi	2 Cc.	30 minims.
Spiritus Juniperi Compositus	8 Cc.	2 fluidrachm
Spiritus Lavandulæ	2 Cc.	30 minims.
Spiritus Menthæ Piperitæ	2 Cc.	30 minims.
Spiritus Menthæ Viridis	2 Cc.	30 minims.
Staphisagria	0.065 Gm.	1 grain.
Stillingia	2 Gm.	30 grains.
Stramonium	0.065 Gm.	1 grain.
Strontii Bromidum	1 Gm.	15 grains.
Strontii Iodidum	0.500 Gm.	7½ grains.
Strontii Salicylas	1 Gm.	15 grains.
Strophanthinum	0.3 milligramme.	1/200 grain.
Strophanthus	0.065 Gm.	1 grain.
Strychnina	1 milligramme.	1/64 grain.
Strychninæ Nitras	1 milligramme.	1/64 grain.
Strychninæ Sulphas	1 milligramme.	1/64 grain.
Styrax	1 Gm.	15 grains.
Sulphonethylmethanum	1 Gm.	15 grains.
Sulphonmethanum	1 Gm.	15 grains.
Sulphur Lotum	4 Gm.	60 grains.
Sulphur Præcipitatum	4 Gm.	60 grains.

AVERAGE DOSES, AS GIVEN BY THE U. S. PHARMACOPŒIA, EIGHTH DECENNIAL REVISION.—*Continued.*

PREPARATION.	AVERAGE DOSE.	
		Approximate Equivalent Ordinary System.
Sulphur Sublimatum	4 Gm.	60 grains.
Sumbul	2 Gm.	30 grains.
Syrupus Acidi Hydriodici	4 Cc.	1 fluidrachm
Syrupus Amygdalæ	4 Cc.	1 fluidrachm
Syrupus Calcii Lactophosphatis	8 Cc.	2 fluidrachm
Syrupus Calcis	2 Cc.	30 minims.
Syrupus Ferri Iodidi	1 Cc.	15 minims.
Syrupus Ferri, Quininæ et Strychninæ Phosphatum	4 Cc.	1 fluidrachm
Syrupus Hypophosphitum	8 Cc.	2 fluidrachm
Syrupus Hypophosphitum Compositus	8 Cc.	2 fluidrachm
Syrupus Ipecacuanhæ Emetic	1 Cc.	15 minims.
Expectorant	15 Cc.	4 fluidrachm
Syrupus Krameriæ	4 Cc.	1 fluidrachm
Syrupus Lactucarii	8 Cc.	2 fluidrachm
Syrupus Picis Liquidæ	4 Cc.	1 fluidrachm
Syrupus Pruni Virginianæ	4 Cc.	1 fluidrachm
Syrupus Rhei	8 Cc.	2 fluidrachm
Syrupus Rhei Aromaticus	8 Cc.	2 fluidrachm
Syrupus Rubi	4 Cc.	1 fluidrachm
Syrupus Sarsaparillæ Compositus	16 Cc.	4 fluidrachm
Syrupus Scillæ	2 Cc.	30 minims.
Syrupus Scillæ Compositus	2 Cc.	30 minims.
Syrupus Senegæ	4 Cc.	1 fluidrachm
Syrupus Sennæ	4 Cc.	1 fluidrachm
Syrupus Tolutanus	16 Cc.	4 fluidrachm
Syrupus Zingiberis	16 Cc.	4 fluidrachm
Tamarindus	16 Gm.	240 grains.
Taraxacum	8 Gm.	120 grains.
Terebenum	0.5 Cc.	8 minims.
Terpini Hydras	0.125 Gm.	2 grains.
Thymol	0.125 Gm.	2 grains.
Tinctura Aconiti	0.6 Cc.	10 minims.
Tinctura Aloes	2 Cc.	30 minims.
Tinctura Aloes et Myrrhæ	2 Cc.	30 minims.
Tinctura Arnicæ	1 Cc.	15 minims.
Tinctura Asafœtidæ	1 Cc.	15 minims.
Tinctura Aurantii Amari	4 Cc.	1 fluidrachm
Tinctura Aurantii Dulcis	4 Cc.	1 fluidrachm.
Tinctura Belladonnæ Foliorum	0.5 Cc.	8 minims.
Tinctura Benzoini	1 Cc.	15 minims.
Tinctura Benzoini Composita	2 Cc.	30 minims.
Tinctura Calumbæ	4 Cc.	1 fluidrachm.
Tinctura Cannabis Indicæ	0.6 Cc.	10 minims.

AVERAGE DOSES, AS GIVEN BY THE U. S. PHARMACOPŒIA, EIGHTH DECENNIAL REVISION.—*Continued.*

PREPARATION.	AVERAGE DOSE.	
	Metric System.	Approximate Equivalent Ordinary System.
Tinctura Cantharidis	0.3 Cc.	5 minims.
Tinctura Capsici	0.5 Cc.	8 minims.
Tinctura Cardamomi	4 Cc.	1 fluidrachm.
Tinctura Cardamomi Composita	4 Cc.	1 fluidrachm.
Tinctura Cimicifugæ	4 Cc.	1 fluidrachm.
Tinctura Cinchonæ	4 Cc.	1 fluidrachm.
Tinctura Cinchonæ Composita	4 Cc.	1 fluidrachm.
Tinctura Cinnamomi	2 Cc.	30 minims.
Tinctura Colchici Seminis	2 Cc.	30 minims.
Tinctura Digitalis	1 Cc.	15 minims.
Tinctura Ferri Chloridi	0.5 Cc.	8 minims
Tinctura Gallæ	4 Cc.	1 fluidrachm.
Tinctura Gambir Composita	4 Cc.	1 fluidrachm.
Tinctura Gelsemii	0.5 Cc.	8 minims.
Tinctura Gentianæ Composita	4 Cc.	1 fluidrachm.
Tinctura Guaiaci	4 Cc.	1 fluidrachm.
Tinctura Guaiaci Ammoniata	2 Cc.	30 minims.
Tinctura Hydrastis	4 Cc.	1 fluidrachm.
Tinctura Hyoscyami	1 Cc.	15 minims.
Tinctura Iodi	0.1 Cc.	1½ minims.
Tinctura Ipecacuanhæ et Opii	0.5 Cc.	8 minims.
Tinctura Kino	4 Cc.	1 fluidrachm.
Tinctura Krameriæ	4 Cc.	1 fluidrachm.
Tinctura Lactucarii	2 Cc.	30 minims.
Tinctura Lavandulæ Composita	2 Cc.	30 minims.
Tinctura Lobelæ Expectorant	1 Cc.	15 minims.
Emetic	4 Cc.	1 fluidrachm.
Tinctura Moschi	4 Cc.	1 fluidrachm.
Tinctura Myrrhæ	1 Cc.	15 minims.
Tinctura Nucis Vomicæ	0.6 Cc.	10 minims.
Tinctura Opii	0.5 Cc.	8 minims.
Tinctura Opii Camphorata	8 Cc.	2 fluidrachms
Tinctura Opii Deodorati	0.5 Cc.	8 minims.
Tinctura Physostigmatis	1 Cc.	15 minims.
Tinctura Quassiæ	2 Cc.	30 minims.
Tinctura Rhei	4 Cc.	1 fluidrachm.
Tinctura Rhei Aromatica	2 Cc.	30 minims.
Tinctura Sanguinariæ	1 Cc.	15 minims.
Tinctura Scillæ	1 Cc.	15 minims.
Tinctura Serpentariæ	4 Cc.	1 fluidrachm.
Tinctura Stramonii	0.5 Cc.	8 minims.
Tinctura Strophanthi	0.5 Cc.	8 minims.
Tinctura Tolutana	2 Cc.	30 minims.
Tinctura Valerianæ	4 Cc.	1 fluidrachm.
Tinctura Valerianæ Ammoniata	2 Cc.	30 minims.
Tinctura Veratri	1 Cc.	15 minims.
Tinctura Zingiberis	2 Cc.	30 minims.

Average Doses, as Given by the U. S. Pharmacopœia, Eighth Decennial Revision.—*Continued.*

Preparation.	Average Dose.	
	Metric System.	Approximate Equivalent Ordinary System.
Triticum	8 Gm.	120 grains.
Trituratio Elaterini	0.030 Gm.	½ grain.
Uva Ursi	2 Gm.	30 grains.
Valeriana	2 Gm.	30 grains.
Vanilla	1 Gm.	15 grains.
Vanillinum	0.030 Gm.	½ grain.
Veratrina	2 milligrammes.	1/30 grain.
Veratrum	0.125 Gm.	2 grains.
Viburnum Opulus	2 Gm.	30 grains.
Viburnum Prunifolium	2 Gm.	30 grains.
Vinum Antimonii	1 Cc.	15 minims.
Vinum Cocæ	16 Cc.	4 fluidrachms
Vinum Colchici Seminis	2 Cc.	30 minims.
Vinum Ergotæ	8 Cc.	2 fluidrachms
Vinum Ferri	8 Cc.	2 fluidrachms
Vinum Ferri Amarum	8 Cc.	2 fluidrachms
Vinum Ipecacuanhæ	1 Cc.	15 minims.
Vinum Opii	0.5 Cc.	8 minims.
Xanthoxylum	2 Gm.	30 grains.
Zinci Acetas	0.125 Gm.	2 grains.
Zinci Bromidum	0.125 Gm.	2 grains.
Zinci Iodidum	0.065 Gm.	1 grain.
Zinci Oxidum	0.250 Gm.	4 grains.
Zinci Phenolsulphonas	0.125 Gm.	2 grains.
Zinci Sulphas ....Emetic..	1 Gm.	15 grains.
Zinci Valeras	0.125 Gm.	2 grains.
Zingiber	1 Gm.	15 grains.

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ARRANGED ALPHABETICALLY BY AUTHORS' NAMES.

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